

# Kinetics and Mechanism of Anilinolyses of Ethyl Methyl, Ethyl Propyl and Diisopropyl Chlorothiophosphates in Acetonitrile

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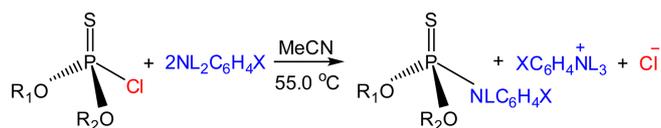
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Nucleophilic substitution reactions of ethyl methyl (**2**), ethyl propyl (**4**) and diisopropyl (**7**) chlorothiophosphates with substituted anilines and deuterated anilines are investigated kinetically in acetonitrile at 55.0 °C. A concerted mechanism is proposed based on the selectivity parameters. The deuterium kinetic isotope effects (DKIEs;  $k_{\text{H}}/k_{\text{D}}$ ) are secondary inverse ( $k_{\text{H}}/k_{\text{D}} = 0.66\text{--}0.99$ ) with **2**, primary normal and secondary inverse ( $k_{\text{H}}/k_{\text{D}} = 0.78\text{--}1.19$ ) with **4**, and primary normal ( $k_{\text{H}}/k_{\text{D}} = 1.06\text{--}1.21$ ) with **7**. The primary normal and secondary inverse DKIEs are rationalized by frontside attack involving hydrogen bonded, four-center-type transition state, and backside attack involving in-line-type transition state, respectively. The anilinolyses of ten chlorothiophosphates are examined based on the reactivity, steric effect of the two ligands, thio effect, reaction mechanism, DKIE and activation parameter.

**Key Words** : Thiophosphoryl transfer reaction, Anilinolysis, Chlorothiophosphate, Deuterium kinetic isotope effect, Steric effect

## Introduction

To extend the kinetic studies on the anilinolysis of chlorothiophosphates, the reactions of ethyl methyl (**2**), ethyl propyl (**4**) and diisopropyl (**7**) chlorothiophosphates with substituted anilines ( $\text{XC}_6\text{H}_4\text{NH}_2$ ) and deuterated anilines ( $\text{XC}_6\text{H}_4\text{ND}_2$ ) are investigated kinetically in acetonitrile (MeCN) at  $55.0 \pm 0.1$  °C (Scheme 1). The aim is to obtain further information on thiophosphoryl transfer reactions by comparing the anilinolyses of the following chlorothiophosphates in terms of the reactivities, steric effects, thio effects, reaction mechanisms, deuterium kinetic isotope effects (DKIEs) and activation parameters: dimethyl [**1**:  $(\text{MeO})_2\text{P}(=\text{S})\text{Cl}$ ],<sup>1</sup> diethyl [**3**:  $(\text{EtO})_2\text{P}(=\text{S})\text{Cl}$ ],<sup>1</sup> dipropyl [**5**:  $(\text{PrO})_2\text{P}(=\text{S})\text{Cl}$ ],<sup>2</sup> dibutyl [**6**:  $(\text{BuO})_2\text{P}(=\text{S})\text{Cl}$ ],<sup>3</sup> Y-aryl ethyl [**8**:  $(\text{EtO})(\text{YC}_6\text{H}_4\text{O})\text{P}(=\text{S})\text{Cl}$ ],<sup>4</sup> Y-aryl phenyl [**9**:  $(\text{PhO})(\text{YC}_6\text{H}_4\text{O})\text{P}(=\text{S})\text{Cl}$ ],<sup>5</sup> and Y-aryl 4-chlorophenyl [**10**:  $(4\text{-ClC}_6\text{H}_4\text{O})(\text{YC}_6\text{H}_4\text{O})\text{P}(=\text{S})\text{Cl}$ ],<sup>5</sup> chlorothiophosphates. **1-10** are numbered according to the sequence of the summation of the Taft steric constants of the two ligands ( $\text{R}_1$  and  $\text{R}_2$ ).<sup>6,7</sup>



$\text{R}_1 = \text{Me}$ ,  $\text{R}_2 = \text{Et}$  (**2**);  $\text{R}_1 = \text{Et}$ ,  $\text{R}_2 = \text{Pr}$  (**4**);  $\text{R}_1 = \text{R}_2 = i\text{-Pr}$  (**7**)

$\text{L} = \text{H}$ ,  $\text{D}$ ;  $\text{X} = 4\text{-MeO}$ ,  $4\text{-Me}$ ,  $3\text{-Me}$ ,  $\text{H}$ ,  $3\text{-MeO}$ ,  $4\text{-Cl}$ ,  $3\text{-Cl}$

**Scheme 1.** Anilinolyses of ethyl methyl (**2**), ethyl propyl (**4**) and diisopropyl (**7**) chlorothiophosphates in MeCN at 55.0 °C.

## Results and Discussion

The observed pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) were

found to follow Eq. (1) for all reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The  $k_0$  values were negligible ( $k_0 \approx 0$ ) in MeCN. The second-order rate constants ( $k_{\text{H}}$  and  $k_{\text{D}}$ ) were determined for at least five concentrations of the anilines. The linear plots of Eq. (1) confirm the absence of base-catalysis or noticeable side reactions, and that the overall reaction is described by Scheme 1.

$$k_{\text{obsd}} = k_0 + k_{\text{H(D)}}[\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)] \quad (1)$$

Tables 1-3 summarize the  $k_{\text{H(D)}}$  values, DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ), Hammett  $\rho_{\text{X(H and D)}}$  and Brønsted  $\beta_{\text{X(H and D)}}$  selectivity parameters of the reactions of **2**, **4** and **7**, respectively, with the X-anilines and deuterated X-anilines. The  $\text{p}K_{\text{a}}(\text{X})$  values of

**Table 1.** Second-Order Rate Constants ( $k_{\text{H(D)}} \times 10^4/\text{M}^{-1} \text{s}^{-1}$ ), Selectivity Parameters ( $\rho_{\text{X}}$  and  $\beta_{\text{X}}$ )<sup>a,b</sup> and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of Ethyl Methyl Chlorothiophosphate (**2**) with  $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$  in MeCN at 55.0 °C

X	$k_{\text{H}} \times 10^4$	$k_{\text{D}} \times 10^4$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	$37.7 \pm 0.3$	$38.0 \pm 0.3$	$0.992 \pm 0.011^c$
4-Me	$22.0 \pm 0.1$	$22.6 \pm 0.1$	$0.973 \pm 0.006$
3-Me	$13.6 \pm 0.1$	$15.1 \pm 0.1$	$0.901 \pm 0.009$
H	$8.44 \pm 0.01$	$9.86 \pm 0.02$	$0.856 \pm 0.002$
3-MeO	$5.07 \pm 0.01$	$6.65 \pm 0.07$	$0.762 \pm 0.008$
4-Cl	$2.75 \pm 0.01$	$3.81 \pm 0.04$	$0.722 \pm 0.008$
3-Cl	$1.39 \pm 0.01$	$2.11 \pm 0.01$	$0.659 \pm 0.006$
$\rho_{\text{X(H)}}^a = -2.24 \pm 0.02$		$\rho_{\text{X(D)}}^a = -1.94 \pm 0.02$	
$\beta_{\text{X(H)}}^a = 0.79 \pm 0.05$		$\beta_{\text{X(D)}}^a = 0.69 \pm 0.04$	

<sup>a</sup>The  $\sigma$  and  $\text{p}K_{\text{a}}$  values of X-anilines in water were taken from refs. 15 and 16, respectively. <sup>b</sup>Correlation coefficients ( $r$ ) of  $\rho_{\text{X}}$  and  $\beta_{\text{X}}$  values are better than 0.996. <sup>c</sup>Standard error  $\{= 1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2 \times (\Delta k_{\text{D}})^2]^{1/2}\}$  from ref. 17.

**Table 2.** Second-Order Rate Constants ( $k_{\text{H(D)}} \times 10^4/\text{M}^{-1} \text{s}^{-1}$ ), Selectivity Parameters ( $\rho_{\text{X}}$  and  $\beta_{\text{X}}$ )<sup>a</sup> and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of Ethyl Propyl Chlorothiophosphate (**4**) with  $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$  in MeCN at 55.0 °C

X	$k_{\text{H}} \times 10^4$	$k_{\text{D}} \times 10^4$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	31.5 ± 0.2	40.3 ± 0.3	0.782 ± 0.006
4-Me	14.3 ± 0.1	17.4 ± 0.2	0.822 ± 0.011
3-Me	6.50 ± 0.02	7.64 ± 0.02	0.851 ± 0.006
H	3.89 ± 0.02	4.16 ± 0.01	0.935 ± 0.005
3-MeO	3.83 ± 0.01	3.59 ± 0.01	1.07 ± 0.01
4-Cl	1.44 ± 0.01	1.28 ± 0.02	1.13 ± 0.02
3-Cl	0.498 ± 0.001	0.418 ± 0.001	1.19 ± 0.01
$\rho_{\text{X(H)}}^a = -2.62 \pm 0.11$		$\rho_{\text{X(D)}}^a = -2.94 \pm 0.10$	
$\beta_{\text{X(H)}}^a = 0.93 \pm 0.11$		$\beta_{\text{X(D)}}^a = 1.04 \pm 0.10$	

<sup>a</sup>Correlation coefficients (r) of  $\rho_{\text{X}}$  and  $\beta_{\text{X}}$  values are better than 0.984.**Table 3.** Second-Order Rate Constants ( $k_{\text{H(D)}} \times 10^4/\text{M}^{-1} \text{s}^{-1}$ ), Selectivity Parameters ( $\rho_{\text{X}}$  and  $\beta_{\text{X}}$ )<sup>a</sup> and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of Diisopropyl Chlorothiophosphate (**7**) with  $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$  in MeCN at 55.0 °C

X	$k_{\text{H}} \times 10^4$	$k_{\text{D}} \times 10^4$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	10.4 ± 0.1	9.80 ± 0.05	1.06 ± 0.01
4-Me	5.80 ± 0.04	5.35 ± 0.04	1.08 ± 0.01
3-Me	2.97 ± 0.03	2.70 ± 0.03	1.10 ± 0.01
H	2.02 ± 0.01	1.82 ± 0.02	1.11 ± 0.01
3-MeO	1.02 ± 0.01	0.890 ± 0.006	1.15 ± 0.01
4-Cl	0.590 ± 0.003	0.510 ± 0.005	1.16 ± 0.02
3-Cl	0.270 ± 0.003	0.224 ± 0.002	1.21 ± 0.02
$\rho_{\text{X(H)}}^a = -2.47 \pm 0.02$		$\rho_{\text{X(D)}}^a = -2.55 \pm 0.02$	
$\beta_{\text{X(H)}}^a = 0.87 \pm 0.03$		$\beta_{\text{X(D)}}^a = 0.90 \pm 0.03$	

<sup>a</sup>Correlation coefficients (r) of  $\rho_{\text{X}}$  and  $\beta_{\text{X}}$  values are better than 0.999.

the X-anilines in water were used to obtain the Brønsted  $\beta_{\text{X}}$  values in MeCN, and this procedure was justified experimentally and theoretically.<sup>8-11</sup> The  $\text{p}K_{\text{a}}(\text{X})$  and  $\sigma_{\text{X}}$  values of the deuterated X-anilines are assumed to be identical to those of the X-anilines. Perrin *et al.* reported that the basicities of  $\beta$ -deuterated analogs of benzylamine, *N,N*-dimethylaniline and

methylamine increase approximately by 0.02  $\text{p}K_{\text{a}}$  units per deuterium, and that these effects are additive.<sup>12-14</sup> Therefore, the  $\text{p}K_{\text{a}}(\text{X})$  values of deuterated X-anilines might be slightly higher than those of X-anilines, but the difference is too small to be considered. The stronger nucleophile leads to a faster rate, as observed in a typical nucleophilic substitution reaction with a partial positive charge development at the nucleophilic N atom in the transition state (TS). The magnitudes of the  $\beta_{\text{X(H)}}$  values are relatively large; 0.79, 0.93 and 0.87 for **2**, **4** and **7**, respectively. The DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) are secondary inverse ( $k_{\text{H}}/k_{\text{D}} = 0.66-0.99$ ) with **2**, primary normal and secondary inverse ( $k_{\text{H}}/k_{\text{D}} = 0.78-1.19$ ) with **4**, and primary normal ( $k_{\text{H}}/k_{\text{D}} = 1.06-1.21$ ) with **7**.

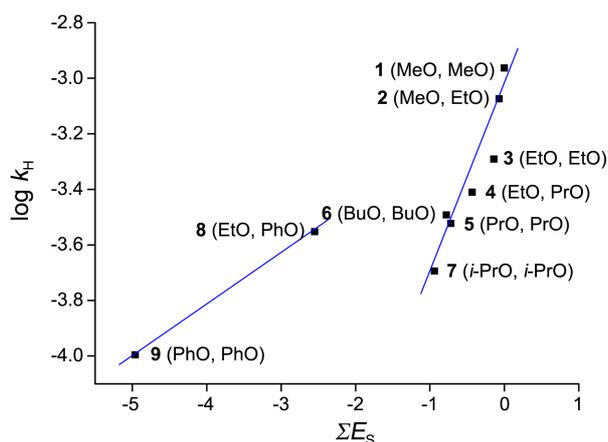
Table 4 summarizes the second-order rate constants ( $k_{\text{H}}$ ) with unsubstituted aniline, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory using the Gaussian 03 program], summations of the Taft steric constants of  $\text{R}_1$  and  $\text{R}_2$  [ $\Sigma E_{\text{S}} = E_{\text{S}}(\text{R}_1) + E_{\text{S}}(\text{R}_2)$ ],<sup>6,7</sup> Brønsted coefficients ( $\beta_{\text{X(H)}}$ ), cross-interaction constants (CICs;  $\rho_{\text{XY}}$ ),<sup>18-20</sup> DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) and variation trends of the  $k_{\text{H}}/k_{\text{D}}$  values with the substituent X in the nucleophiles for the reactions of **1-10** with  $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$  in MeCN at 55.0 °C. The variation trends of the  $k_{\text{H}}/k_{\text{D}}$  values with X are represented by an arrow. The vertical arrows ( $\uparrow$  or  $\downarrow$ ) indicate the direction of the consistent increase in  $k_{\text{H}}/k_{\text{D}}$  value with X. For example,  $\uparrow$  indicates that the  $k_{\text{H}}/k_{\text{D}}$  value increases with a stronger nucleophile.

**Reactivity and Steric Effect.** The observed sequence of the anilinolysis rates is not consistent with the expectations for the positive NBO charge at the reaction center P atom, suggesting that the inductive effects of the two ligands are not a major factor determining the anilinolysis rates of the chlorothiophosphates. The sequence of the anilinolysis rates is almost inversely proportional to the size of the two ligands, but could be divided into two groups; *a* group of **1-7** containing two alkoxy ligands and *b* group of **8** and **9** containing phenoxy ligand(s).<sup>21</sup> The steric effects of the two ligands on the anilinolysis rates of the P=O counterparts, chlorophosphates [( $\text{R}_1\text{O}$ )( $\text{R}_2\text{O}$ )P(=O)Cl-type], show similar

**Table 4.** Summary of the Second-Order Rate Constants ( $k_{\text{H}} \times 10^4/\text{M}^{-1} \text{s}^{-1}$ ) with  $\text{C}_6\text{H}_5\text{NH}_2$ , NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants of  $\text{R}_1$  and  $\text{R}_2$  [ $\Sigma E_{\text{S}} = E_{\text{S}}(\text{R}_1) + E_{\text{S}}(\text{R}_2)$ ], Brønsted Coefficients ( $\beta_{\text{X(H)}}$ ), CICs ( $\rho_{\text{XY}}$ ), DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) and Variation Trends of  $k_{\text{H}}/k_{\text{D}}$  Values with X for the Reactions of **1-10** with  $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$  in MeCN at 55.0 °C

substrate	$10^4 k_{\text{H}}^a$	charge at P	$-\Sigma E_{\text{S}}^b$	$\beta_{\text{X(H)}}$	$\rho_{\text{XY}}$	$k_{\text{H}}/k_{\text{D}}$	trend
<b>1:</b> (MeO) <sub>2</sub> P(=S)Cl	10.9	1.687	0.00	0.99	–	0.95-1.06	$\uparrow$
<b>2:</b> (MeO)(EtO)P(=S)Cl	8.44	1.693	0.07	0.79	–	0.66-0.99	$\uparrow$
<b>3:</b> (EtO) <sub>2</sub> P(=S)Cl	5.12	1.701	0.14	0.98	–	1.01-1.10	$\uparrow$
<b>4:</b> (EtO)(PrO)P(=S)Cl	3.89	1.700	0.43	0.93	–	0.78-1.19	$\downarrow$
<b>5:</b> (PrO) <sub>2</sub> P(=S)Cl	3.00	1.702	0.72	1.14	–	1.11-1.35	$\downarrow$
<b>6:</b> (BuO) <sub>2</sub> P(=S)Cl	3.22	1.703	0.78	1.17	–	1.10-1.35	$\downarrow$
<b>7:</b> ( <i>i</i> -PrO) <sub>2</sub> P(=S)Cl	2.02	1.723	0.94	0.87	–	1.06-1.21	$\downarrow$
<b>8:</b> (EtO)(YC <sub>6</sub> H <sub>4</sub> O)P(=S)Cl	2.80 <sup>c</sup>	1.687 <sup>c</sup>	2.55 <sup>c</sup>	1.10-1.19	–0.28	1.06-1.27	$\downarrow$
<b>9:</b> (PhO)(YC <sub>6</sub> H <sub>4</sub> O)P(=S)Cl	1.01 <sup>c</sup>	1.661 <sup>c</sup>	4.96 <sup>c</sup>	1.34-1.41	–0.22	1.11-1.33	$\downarrow$
<b>10:</b> (4-CIC <sub>6</sub> H <sub>4</sub> O)(YC <sub>6</sub> H <sub>4</sub> O)P(=S)Cl	1.48 <sup>c</sup>	1.667 <sup>c</sup>	~4.96 <sup>c</sup>	1.23-1.38	–0.50	1.10-1.46	$\downarrow$

<sup>a</sup>Values with unsubstituted aniline at 55.0 °C. <sup>b</sup>Note that the values of the  $\Sigma E_{\text{S}}$  are not ' $E_{\text{S}}(\text{R}_1\text{O}) + E_{\text{S}}(\text{R}_2\text{O})$ ' but ' $E_{\text{S}}(\text{R}_1) + E_{\text{S}}(\text{R}_2)$ ' because of the lack of data of Taft steric constants of  $\text{R}_i\text{O}$ . <sup>c</sup>Values with Y = H.



**Figure 1.** Taft plot of  $\log k_H$  vs  $\Sigma E_S$  for the reactions of **1-9** with  $C_6H_5NH_2$  in MeCN at 55.0 °C. The number of the substrate and two ligands of  $R_1O$  and  $R_2O$  are displayed next to the corresponding point.

trends to those of the chlorothiophosphates.<sup>1-4,22,26</sup> The greater the size of the two ligands, the rate becomes slower. This suggests that the steric effects of the two ligands play an important role in determining the anilinolysis rates of both the P=S systems (chlorothiophosphates) and P=O counterparts (chlorophosphates). Moreover, the steric effects of the two ligands on the rate in the *a* group are essentially 'different' from those in the *b* group.

The Taft Eq. of ' $\log k_H = \delta \Sigma E_S + C$ ' might be used to rationalize the steric effects of the two ligands on the reaction rate.<sup>6</sup> The  $\Sigma E_S$  value is not ' $E_S(R_1O) + E_S(R_2O)$ ' but ' $E_S(R_1) + E_S(R_2)$ ' because the data of the Taft steric constant of  $R_1O$  are unavailable; [ $E_S = 0(\text{Me}), -0.07(\text{Et}), -0.36(\text{Pr}), -0.39(\text{Bu}), -0.47(i\text{-Pr}), -2.48(\text{Ph})$ ]. Figure 1 shows the Taft plot of  $\log k_H$  with unsubstituted aniline ( $C_6H_5NH_2$ ) versus the summation of the Taft steric constants of the two ligands for the anilinolyses of nine chlorothiophosphates (**1-9**) in MeCN at 55.0 °C, giving sensitivity coefficients of  $\delta = 0.65 \pm 0.09$  ( $r = 0.948$ ) and  $\delta = 0.18$  with seven substrates of **1-7** (*a* group) and two substrates of **8** and **9** (*b* group), respectively.

The sensitivity coefficients of  $\delta = 0.59 \pm 0.18$  ( $r = 0.847$ ) with five P=O counterparts of **1**, **3** and **5-7** (*a* group) and  $\delta = 0.15$  with two P=O counterparts of **8** and **9** (*b* group) were

obtained in MeCN at 55.0 °C, as shown in Fig. R1.<sup>27</sup> The  $\delta$  values of the P=S systems are somewhat larger than their P=O counterparts, suggesting that the P=S systems are slightly more sensitive to the steric effects of the two ligands on the rate than their P=O counterparts.

**Thio Effect.** The anilinolysis rates of the P=O systems are 4-9 times faster than their P=S counterparts, as shown in Table 5. P=O systems are generally more reactive than their P=S counterparts for several reasons, the so-called 'thio effect', which is mainly the difference in electronegativity between O and S and favors P=O over P=S system.<sup>28-31</sup> Ormazabal-Toledo and his coworkers also reported thio-effect in carbonyl derivatives.<sup>32</sup> The differences in the NBO charges at the reaction center P atom between the P=O and P=S systems [(NBO charge at P atom) = (NBO charge at P atom of the P=O system) - (NBO charge at P atom of the P=S system)] are almost constant in the range of 0.54-0.57 in the gas phase.<sup>33</sup>

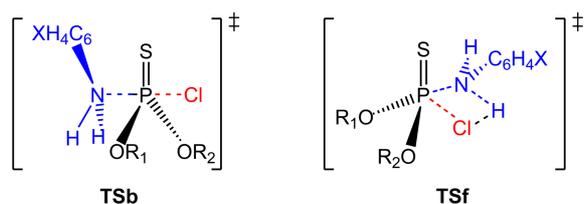
**Reaction Mechanism.** Focus will now shift to the anilinolysis mechanism of the chlorothiophosphates. The negative  $\rho_{XY}$  values of **8** ( $\rho_{XY} = -0.28$ ), **9** ( $\rho_{XY} = -0.22$ ) and **10** ( $\rho_{XY} = -0.50$ ) imply that the reactions proceed through a concerted  $S_N2$  mechanism,<sup>34</sup> despite the considerably large  $\beta_{X(H)}$  values of 1.1-1.4. The  $\beta_{X(H)}$  values of **1-7** are in the range of 0.8-1.2, which are somewhat smaller or comparable to those of **8-10**. The authors suggest that the anilinolyses of **1-7** proceed through a concerted  $S_N2$  mechanism. The relatively large  $\beta_X$  values are typical of the anilinolyses of the chlorothiophosphates, even though the reactions proceed through a concerted  $S_N2$  mechanism.

**Deuterium Kinetic Isotope Effect.** The DKIEs have provided a useful means of determining the TS structures in the nucleophilic substitution reactions, and how the reactants alter the TS structures, particularly through changes in substituents. The incorporation of deuterium in the nucleophile has an advantage in that the  $\alpha$ -DKIEs reflect only the degree of bond formation. When the partial deprotonation of aniline occurs in a rate-limiting step by hydrogen bonding, the  $k_H/k_D$  values are greater than unity, primary normal ( $k_H/k_D > 1.0$ ).<sup>35-40</sup> The greater the extent of the hydrogen bond, the value of  $k_H/k_D$  becomes greater. In contrast, the DKIEs can only be secondary inverse ( $k_H/k_D < 1.0$ ) in a normal  $S_N2$  reaction, because the N-H(D) vibrational frequencies invariably

**Table 5.** Rate Ratios of the Anilinolyses of the P=O Systems to their P=S Counterparts in MeCN at 55.0 °C, and Differences in the NBO Charge at the P Atom between the P=O and P=S Systems

substrate	$[10^4 k_H(\text{P=O})]/[10^4 k_H(\text{P=S})]$	$\Delta(\text{NBO charge at P})^a$	ref. (P=O;P=S)
<b>1</b> (MeO,MeO)	42.8/10.9 = 3.9	2.226 - 1.687 = 0.539	1;1
<b>3</b> (EtO,EtO)	28.2/5.12 = 5.5	2.236 - 1.701 = 0.535	1;1
<b>5</b> (PrO,PrO)	21.2/3.00 = 7.1	2.239 - 1.702 = 0.537	25;2
<b>6</b> (BuO,BuO)	20.6/3.22 = 6.4	2.239 - 1.703 = 0.536	24;3
<b>7</b> ( <i>i</i> -PrO, <i>i</i> -PrO)	7.10/2.02 = 3.5	2.269 - 1.723 = 0.546	23;this work
<b>8</b> (EtO,PhO)	20.0/2.80 = 7.1	2.233 - 1.687 = 0.546	4;4
<b>9</b> (PhO,PhO)	8.91/1.01 = 8.8	2.230 - 1.661 = 0.569	22;5
<b>10</b> (4-ClC <sub>6</sub> H <sub>4</sub> O,PhO)	12.0/1.48 = 8.1	2.232 - 1.667 = 0.565	26;5

<sup>a</sup>(NBO charge at P) = (NBO charge at P atom of the P=O system) - (NBO charge at P atom of the P=S counterpart).



**Scheme 2.** Backside attack involving in-line-type TSb and frontside attack involving hydrogen bonded, four-center-type TSf.

increase when forming the TS because of an increase in steric congestion in the bond-making process.<sup>41-43</sup> The greater the degree of the steric congestion in the TS, the value of  $k_H/k_D$  becomes smaller.

The DKIEs of **2** are secondary inverse ( $k_H/k_D = 0.66-0.99$ ) and those of **1** ( $k_H/k_D = 0.95-1.06$ ) and **4** ( $k_H/k_D = 0.78-1.19$ ) are both secondary inverse and primary normal. The DKIEs of **3** ( $k_H/k_D = 1.01-1.10$ ), **5** ( $k_H/k_D = 1.11-1.35$ ), **6** ( $k_H/k_D = 1.10-1.35$ ), **7** ( $k_H/k_D = 1.06-1.21$ ), **8** ( $k_H/k_D = 1.06-1.27$ ), **9** ( $k_H/k_D = 1.11-1.33$ ) and **10** ( $k_H/k_D = 1.11-1.33$ ) are primary normal. The  $k_H/k_D$  values of **1-3** increase as the aniline becomes more basic (symbol of  $\uparrow$ ), whereas those of **4-10** decrease as the aniline becomes more basic (symbol of  $\downarrow$ ). The authors could find the consistent correlation between the  $\beta_X$  values and DKIEs, between the reaction mechanism and DKIEs or between the reaction mechanism and variation trends of DKIEs.

The attacking direction of the aniline nucleophile might be divided *semi*-quantitatively into three parts based on the magnitudes of the  $k_H/k_D$  values: (i) predominant backside attack involving in-line-type TSb (Scheme 2) when  $k_H/k_D < 1$ ; (ii) the fraction of frontside attack involving hydrogen bonded, four-center-type TSf (Scheme 2) is greater than that of backside attack TSb when  $1.0 < k_H/k_D < 1.1$ ; and (iii) predominant frontside attack TSf when  $k_H/k_D > 1.1$ .<sup>44</sup>

Therefore, the authors propose the attacking direction of the anilines as follows: in **1**, gradually changing from backside to frontside as the aniline becomes less basic based on  $k_H/k_D = 0.95-1.06$ ; in **2**, predominant backside based on  $k_H/k_D = 0.66-0.99$ ; in **3**, the fraction of the frontside attack TSf is greater than that of backside attack TSb based on  $k_H/k_D = 1.01-1.10$ ; in **4**, gradually changing from frontside to backside as the aniline becomes less basic based on  $k_H/k_D = 0.78-1.19$ ; and in **5-10**, predominant frontside based on  $k_H/k_D = 1.11-1.35$  (**5**),  $1.10-1.35$  (**6**),  $1.06-1.21$  (**7**),  $1.06-1.27$  (**8**),  $1.11-1.33$  (**9**) and  $1.10-1.46$  (**10**). The considerably small value of  $k_H/k_D = 0.66$  of **2** with X = 3-Cl indicates severe steric congestion in the TS.

**Activation Parameter.** The activation parameters, enthalpies and entropies of activation, were determined for the anilinolyses (with  $C_6H_5NH_2$ ) of **2**, **4** and **7**, as shown in Table S1 (supporting information). Table 6 summarizes the activation parameters of the anilinolyses of **1-10**. The enthalpies of activation are relatively low (5-11 kcal mol<sup>-1</sup>) and the entropies of activation are relatively large negative values ( $-39$  to  $-59$  cal mol<sup>-1</sup> K<sup>-1</sup>). The relatively low activation enthalpy and large negative activation entropy are typical for the

**Table 6.** Activation Parameters for the Reactions of **1-10** with Aniline ( $C_6H_5NH_2$ ) in MeCN

substrate	$\Delta H^\ddagger$ /kcal mol <sup>-1</sup>	$-\Delta S^\ddagger$ /cal mol <sup>-1</sup> K <sup>-1</sup>	ref
<b>1</b> : (MeO) <sub>2</sub> P(=S)Cl	8.0	49	1
<b>2</b> : (MeO)(EtO)P(=S)Cl	11.2	39	this work
<b>3</b> : (EtO) <sub>2</sub> P(=S)Cl	6.0	55	1
<b>4</b> : (EtO)(PrO)P(=S)Cl	7.3	52	this work
<b>5</b> : (PrO) <sub>2</sub> P(=S)Cl	7.3	53	2
<b>6</b> : (BuO) <sub>2</sub> P(=S)Cl	7.4	52	3
<b>7</b> : ( <i>i</i> -PrO) <sub>2</sub> P(=S)Cl	9.4	47	this work
<b>8</b> : (EtO)(PhO)P(=S)Cl	5.4	59	4
<b>9</b> : (PhO) <sub>2</sub> P(=S)Cl	7.7	54	5
<b>10</b> : (4-ClC <sub>6</sub> H <sub>4</sub> O)(PhO)P(=S)Cl	6.9	55	5

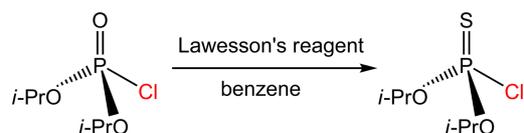
aminolyses of the P=S systems.

In summary, kinetic studies are performed on the anilinolyses of ethyl methyl (**2**), ethyl propyl (**4**) and diisopropyl (**7**) chlorothiophosphates with substituted anilines and deuterated anilines in acetonitrile at  $55.0 \pm 0.1$  °C. The major factor determining the anilinolysis rates of the chlorothiophosphates is the steric effects over the inductive effects of the two ligands, which are divided into two groups; containing alkoxy ligands and phenoxy ligand(s). The anilinolysis rates of the P=O systems are 4-9 times faster than their P=S counterparts because of the so-called 'thio effect'. The relatively large  $\beta_X$  values are typical of the anilinolyses of the chlorothiophosphates, even though the reactions proceed through a concerted S<sub>N</sub>2 mechanism. The authors could not find a consistent correlation between the  $\beta_X$  values and DKIEs, between the reaction mechanism and DKIEs or between the reaction mechanism and variation trends of the DKIEs. The relatively low activation enthalpy and large negative activation entropy are typical for the aminolyses of P=S systems.

## Experimental Section

**Materials.** HPLC grade acetonitrile (water content < 0.005%) was used as received for the kinetic studies. The anilines were redistilled or recrystallized prior to use. Deuterated anilines were synthesized by heating the anilines with deuterium oxide (99.9 atom %D) and one drop of HCl as a catalyst at 85 °C for 72 h. After more than five attempts, > 98% of the anilines were deuterated, as confirmed by <sup>1</sup>H NMR. 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]. Diisopropyl chlorothiophosphate (**7**) was prepared *via* one step synthetic route. Benzene solution of Lawesson's reagent [1,3,2,4-dithiadiphosphetane, 2,4-bis(4-methoxyphenyl)-2,4-disulfide] (10 equiv.) and diisopropyl chlorophosphate

was boiled for on hr.



The reaction mixture was cooled to room temperature, and hexane was added. After filtration, the solvent was evaporated and a yellow liquid was isolated by column chromatography [silica gel, heptane/EtOAc (95:15)]. The analytical and spectroscopic data of the substrates gave the following results (supporting information):

**(MeO)(EtO)P(=S)Cl.** Colorless liquid;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  1.39-1.43 (aliphatic, 3H, t), 3.85-3.93 (aliphatic, 3H, s), 4.27-4.32 (aliphatic, 2H, q);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  15.61, 55.39, 66.34;  $^{31}\text{P-NMR}$  (162 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  81.72 (1P, s, P=S); GC-MS (EI,  $m/z$ ) 174 ( $\text{M}^+$ ).

**(EtO)(PrO)P(=S)Cl.** Colorless liquid;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  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, q);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  9.97, 15.62, 23.16, 66.09, 71.47;  $^{31}\text{P-NMR}$  (162 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  74.42 (1P, s, P=S); GC-MS (EI,  $m/z$ ) 202 ( $\text{M}^+$ ).

**(*i*-PrO) $_2$ P(=S)Cl.** Yellow liquid;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30-1.43 (d, 12H, 4  $\text{CH}_3$ , *i*-PrO), 4.77-4.88 (m, 2H, 2OCH, *i*-PrO);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.25-23.63, 73.91, 74.71;  $^{31}\text{P NMR}$  (162 MHz,  $\text{CDCl}_3$ )  $\delta$  81.02 (s, 1P, P=S); MS (EI)  $m/z$ , 216 ( $\text{M}^+$ ).

**Kinetic Measurements.** The 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. The pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) were measured by curve fitting analysis in origin program with a large excess of anilines: [substrate] =  $5 \times 10^{-3}$  M and [X-aniline] = (0.1-0.3) M for **2** and **4**; [substrate] =  $1 \times 10^{-3}$  M and [X-aniline] = (0.1-0.5) M for **7**. The second-order rate constants ( $k_{\text{H}}$  and  $k_{\text{D}}$ ) were obtained from the slope of a plot of  $k_{\text{obsd}}$  vs [X-aniline or deuterated X-aniline] with at least five concentrations of anilines. The pseudo-first-order rate constant values ( $k_{\text{obsd}}$ ) were an average of at least three runs that were reproducible within  $\pm 3\%$ .

**Product Analysis.** Ethyl methyl (**2**) and ethyl propyl (**4**) chlorothiophosphates were reacted with excess aniline for more than 15 half-lives at 55.0 °C in MeCN. Diisopropyl chlorothiophosphate (**7**) was reacted with an excess 4-methylaniline for more than 15 half-lives at 55.0 °C in MeCN. The aniline hydrochloride and 4-methylaniline hydrochloride salt were separated by filtration. Acetonitrile was removed under reduced pressure. The product was isolated by a treatment with ether and dilute HCl solution using a work up process, and then dried over  $\text{MgSO}_4$ . After filtration the product was isolated by evaporating the solvent under reduced pressure. The analytical data of the products are summarized as follows (supporting information):

**(MeO)(EtO)P(=S)NHC $_6$ H $_5$ .** Liquid;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  1.21-1.39 (aliphatic, 3H, t), 3.64-3.82 (aliphatic, 2H, q), 4.01 (aliphatic, 3H, br., s), 4.11-4.19 (aliphatic, 1H, d), 6.71-7.19 (aromatic, 5H, m);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  15.59, 55.43, 66.36, 115.53-145.51;  $^{31}\text{P-NMR}$  (162 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  13.97 (1P, s, P=S); GC-MS (EI,  $m/z$ ) 231 ( $\text{M}^+$ ).

**(EtO)(PrO)P(=S)NHC $_6$ H $_5$ .** Liquid;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  0.90-0.94 (aliphatic, 3H, t), 1.22-1.45 (aliphatic, 3H, t), 1.64-1.72 (aliphatic, 2H, q), 2.21 (aliphatic, 1H, br., s), 3.69-3.75 (aliphatic, 2H, q), 4.08-4.14 (aliphatic, 2H, m), 6.98-7.00 (aromatic, 3H, m), 7.23-7.26 (aromatic, 2H, t);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  10.01-23.51, 63.25, 68.74, 103.57-139.38;  $^{31}\text{P-NMR}$  (162 MHz,  $\text{CDCl}_3$  & TMS)  $\delta$  70.51 (1P, s, P=S); GC-MS (EI,  $m/z$ ) 259 ( $\text{M}^+$ ).

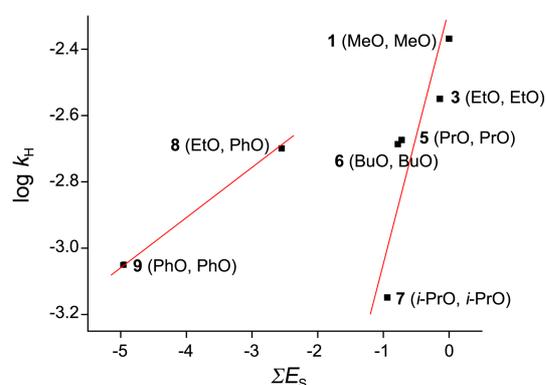
**(*i*-PrO) $_2$ P(=S)NHC $_6$ H $_4$ -4-CH $_3$ .** Brown liquid;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.12-1.43 (d, 12H, 4  $\text{CH}_3$ , *i*-PrO), 2.24 (s, 3H,  $\text{CH}_3$ ), 3.71-3.83 (m, 2H, 2 OCH, *i*-PrO), 5.03 (br, s, 1H, NH), 6.89-7.01 (m, 2H, phenyl), 7.79-7.93 (t,  $J = 8.8$  Hz, 2H, phenyl);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.21-23.58, 23.63, 72.45, 72.50, 117.71, 117.78, 129.59, 129.78;  $^{31}\text{P NMR}$  (162 MHz,  $\text{CDCl}_3$ )  $d$  57.81 (s, 1P, P=S); MS (EI)  $m/z$ , 287 ( $\text{M}^+$ ).

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**Figure R1.** Taft plot of  $\log k_H$  with  $C_6H_5NH_2$  vs  $\Sigma E_S$  for the anilinolyses of the P=O counterparts, chlorophosphates, in MeCN at 55.0 °C. The number of the P=O counterparts and two ligands are displayed next to the corresponding point.

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