

## Kinetics and Mechanism of the Anilinolyses of *O*-Methyl, *O*-Propyl and *O*-Isopropyl Phenyl Phosphonochloridothioates in Acetonitrile

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The kinetic studies on the reactions of *O*-methyl (**1**), *O*-propyl (**3**) and *O*-isopropyl (**4**) phenyl phosphonochloridothioates with substituted anilines and deuterated anilines have been carried out in acetonitrile at 55.0 °C. A concerted S<sub>N</sub>2 mechanism is proposed for the anilinolyses of **1**, **3** and **4**. The anilinolysis rates of the phosphonochloridothioates are predominantly dependent upon the steric effects over the inductive effects of the two ligands. The deuterium kinetic isotope effects (DKIEs;  $k_H/k_D$ ) are primary normal with **1** and **3**, while secondary inverse with **4**. Primary normal and secondary inverse DKIEs are rationalized by frontside and backside nucleophilic attack transition state, respectively. The DKIEs of the phosphonochloridothioates do not have any consistent correlations with the two ligands.

**Key Words** : Thiophosphoryl transfer reaction, Anilinolysis, *O*-Methyl, *O*-propyl and *O*-isopropyl phenyl phosphonochloridothioates, Deuterium kinetic isotope effect

### Introduction

The nucleophilic substitution reactions of tetracoordinate phosphorus involving a leaving group of chloride have been extensively studied in this lab. Two main types of displacement processes are well known in neutral phosphoryl and thiophosphoryl group transfer reactions: the stepwise mechanism (A<sub>N</sub> + D<sub>N</sub>) involving a trigonal bipyramidal pentacoordinate (TBP-5C) intermediate and the concerted displacement (A<sub>N</sub>D<sub>N</sub>) at phosphorus through a single pentacoordinate transition state (TS). To extend the kinetic studies on the anilinolyses of the phosphonochloridothioates, the nucleophilic substitution reactions of *O*-methyl (**1**), *O*-propyl (**3**) and *O*-isopropyl (**4**) phenyl phosphonochloridothioates with anilines (XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>) and deuterated anilines (XC<sub>6</sub>H<sub>4</sub>ND<sub>2</sub>) in acetonitrile (MeCN) at 55.0 ± 0.1 °C (Scheme 1) are investigated kinetically based on the selectivity parameters, steric effects of the two ligands on the rates and deuterium kinetic isotope effects (DKIEs). The purpose of this work is to gain further information on the anilinolyses of the phosphonochloridothioates depending upon the two ligands. The kinetic results of the present work are compared with those of *O*-ethyl [**2**: Ph(EtO)P(=S)Cl],<sup>1</sup> *Y*-*O*-aryl [**5**: Ph(YC<sub>6</sub>H<sub>4</sub>O)P(=S)Cl]<sup>2</sup> and *Y*-*S*-aryl [**6**: Ph(YC<sub>6</sub>H<sub>4</sub>S)P(=S)Cl]<sup>3</sup> phenyl phosphonochloridothioates. The numbering of the substrates follows the sequence of the summation of Taft

steric constants of Ph and R<sub>i</sub>.<sup>4</sup>

### Results and Discussion

The observed pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) were found to follow Eq. (1) for all the 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 ( $k_H$  and  $k_D$ ) were determined for at least five concentrations of anilines. The linear plots of Eq. (1) suggest that there is no base-catalysis or noticeable side reaction and that the overall reaction is described by Scheme 1.

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

Tables 1-3 summarize the  $k_H$  and  $k_D$  values of the reactions of **1**, **3** and **4** with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>), respectively, together with the DKIEs ( $k_H/k_D$ ) and Hammett  $\rho_X$  and Brønsted  $\rho_X$  selectivity parameters. The Brønsted plots [ $\log k_{H(D)}$  vs  $pK_a(X)$ ] for the reactions of **1**, **3** and **4** with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>) are shown in Figs. S25-S27, respectively (supporting information). The  $\beta_X$  values are relatively large:  $\beta_{X(H)} = 1.26, 1.04$  and  $1.10$  with **1**, **3** and **4**, respectively. The primary normal DKIEs ( $k_H/k_D > 1$ ) are observed with all the nucleophiles for the reactions of **1** and **3**, whereas the secondary inverse DKIEs ( $k_H/k_D < 1$ ) are observed with all the nucleophiles for **4**. The values of the primary normal DKIEs invariably increase as the nucleophile becomes less basic for **1** [ $k_H/k_D = 1.08(X = 4\text{-MeO}) \rightarrow 1.17(X = 3\text{-Cl})$ ] and **3** [ $k_H/k_D = 1.02(X = 4\text{-MeO}) \rightarrow 1.48(X = 3\text{-Cl})$ ], while those of the secondary inverse DKIEs invariably increase with a stronger nucleophile for **4** [ $k_H/k_D = 0.63(X = 3\text{-Cl}) \rightarrow 0.99(X = 4\text{-MeO})$ ].

The second-order rate constants ( $k_H$ ) with unsubstituted aniline, natural bond order (NBO) charges at the reaction center P atom [B3LYP/6-311+G(d,p) level of theory] in the



**Scheme 1.** Anilinolyses of *O*-methyl (**1**), *O*-propyl (**3**) and *O*-isopropyl (**4**) phenyl phosphonochloridothioates in MeCN at 55.0 °C.

**Table 1.** Second-Order Rate Constants ( $k_{\text{H(D)}} \times 10^3/\text{M}^{-1}\text{s}^{-1}$ ), 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 *O*-Methyl Phenyl Phosphonochloridithioate (**1**) with  $\text{XC}_6\text{H}_4\text{NH}_2$  ( $\text{D}_2$ ) in MeCN at 55.0 °C

X	$k_{\text{H}} \times 10^3$	$k_{\text{D}} \times 10^3$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	83.2 ± 0.1	76.9 ± 0.1	1.08 ± 0.01 <sup>c</sup>
4-Me	34.7 ± 0.1	31.5 ± 0.1	1.10 ± 0.01
3-Me	12.4 ± 0.1	11.2 ± 0.1	1.11 ± 0.01
H	7.53 ± 0.01	6.53 ± 0.02	1.15 ± 0.01
3-MeO	3.10 ± 0.01	2.63 ± 0.01	1.16 ± 0.01
4-Cl	1.27 ± 0.01	1.09 ± 0.01	1.17 ± 0.01
3-Cl	0.407 ± 0.001	0.347 ± 0.001	1.17 ± 0.01
$\rho_{\text{X(H)}} = -3.57 \pm 0.04$		$\rho_{\text{X(D)}} = -3.63 \pm 0.04$	
$\beta_{\text{X(H)}} = 1.26 \pm 0.05$		$\beta_{\text{X(D)}} = 1.29 \pm 0.05$	

<sup>a</sup>The  $\sigma$  and  $\text{p}K_{\text{a}}$  values of X-anilines in water were taken from refs. 5 and 6, respectively. <sup>b</sup>Correlation coefficients ( $r$ ) of  $\rho_{\text{X}}$  and  $\beta_{\text{X}}$  values are better than 0.998. <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. 7.

**Table 2.** Second-Order Rate Constants ( $k_{\text{H(D)}} \times 10^3/\text{M}^{-1}\text{s}^{-1}$ ), Selectivity Parameters ( $\rho_{\text{X}}$  and  $\beta_{\text{X}}$ )<sup>a</sup> and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of *O*-Propyl Phenyl Phosphonochloridithioate (**3**) with  $\text{XC}_6\text{H}_4\text{NH}_2$  ( $\text{D}_2$ ) in MeCN at 55.0 °C

X	$k_{\text{H}} \times 10^3$	$k_{\text{D}} \times 10^3$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	54.6 ± 0.1	53.4 ± 0.1	1.02 ± 0.01
4-Me	23.4 ± 0.1	19.9 ± 0.1	1.18 ± 0.01
3-Me	9.91 ± 0.04	8.23 ± 0.01	1.20 ± 0.02
H	5.02 ± 0.01	4.03 ± 0.03	1.25 ± 0.01
3-MeO	4.75 ± 0.01	3.62 ± 0.01	1.31 ± 0.01
4-Cl	1.73 ± 0.01	1.26 ± 0.01	1.37 ± 0.01
3-Cl	0.550 ± 0.002	0.373 ± 0.002	1.48 ± 0.10
$\rho_{\text{X(H)}} = -2.94 \pm 0.12$		$\rho_{\text{X(D)}} = -3.16 \pm 0.12$	
$\beta_{\text{X(H)}} = 1.04 \pm 0.12$		$\beta_{\text{X(D)}} = 1.12 \pm 0.13$	

<sup>a</sup>Correlation coefficients ( $r$ ) of  $\rho_{\text{X}}$  and  $\beta_{\text{X}}$  values are better than 0.986.

gas phase, summations of the Taft steric constants of Ph and  $\text{R}_i$  [ $\Sigma E_{\text{S}} = E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i)$ ],<sup>4</sup> Brönsted coefficients ( $\beta_{\text{X(H)}}$ ), cross-interaction constants (CICs;  $\rho_{\text{XY}}$ ),<sup>8</sup> DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) and variation trends of  $k_{\text{H}}/k_{\text{D}}$  values with X for the reactions of **1-6** with  $\text{XC}_6\text{H}_4\text{NH}_2$  ( $\text{D}_2$ ) in MeCN at 55.0 °C are summarized in Table 4. The variation trends of  $k_{\text{H}}/k_{\text{D}}$  values with X are represented with arrow. The vertical arrows ( $\uparrow$  or  $\downarrow$ ) indicate

**Table 4.** 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, Summations of the Taft Steric Constants of Ph and  $\text{R}_i$  [ $\Sigma E_{\text{S}} = E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i)$ ], Brönsted 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 **1-6** with  $\text{XC}_6\text{H}_4\text{NH}_2$  ( $\text{D}_2$ ) in MeCN at 55.0 °C

Substrate	$10^3 k_{\text{H}}^a$	charge at P	$-\Sigma E_{\text{S}}^c$	$\beta_{\text{X(H)}}$	$\rho_{\text{XY}}$	$k_{\text{H}}/k_{\text{D}}$	trend
<b>1:</b> Ph(MeO)P(=S)Cl	7.53	1.472	2.48	1.26	–	1.08-1.17	$\downarrow$
<b>2:</b> Ph(EtO)P(=S)Cl	6.93	1.478	2.55	1.23	–	0.93-1.28	$\downarrow$
<b>3:</b> Ph(PrO)P(=S)Cl	5.02	1.479	2.84	1.04	–	1.02-1.48	$\downarrow$
<b>4:</b> Ph( <i>i</i> -PrO)P(=S)Cl	4.00	1.488	2.95	1.10	–	0.63-0.99	$\uparrow$
<b>5:</b> Ph(YC <sub>6</sub> H <sub>4</sub> O)P(=S)Cl	1.50 <sup>b</sup>	1.462 <sup>b</sup>	4.96	1.22-1.33	-0.38	0.44-1.34	$\downarrow$
<b>6:</b> Ph(YC <sub>6</sub> H <sub>4</sub> S)P(=S)Cl	0.175 <sup>b</sup>	0.999 <sup>b</sup>	–	1.21-1.25	-0.31	0.65-0.98	$\uparrow$

<sup>a</sup>The value with unsubstituted aniline. <sup>b</sup>The value with Y = H. <sup>c</sup>Note that  $\Sigma E_{\text{S}}$  is not ' $E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i\text{O})$ ' but ' $E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i)$ ' due to the lack of data of  $\text{R}_i\text{O}$ .

**Table 3.** Second-Order Rate Constants ( $k_{\text{H(D)}} \times 10^3/\text{M}^{-1}\text{s}^{-1}$ ), Selectivity Parameters ( $\rho_{\text{X}}$  and  $\beta_{\text{X}}$ )<sup>a</sup> and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of *O*-Isopropyl Phenyl Phosphonochloridithioate (**4**) with  $\text{XC}_6\text{H}_4\text{NH}_2$  ( $\text{D}_2$ ) in MeCN at 55.0 °C

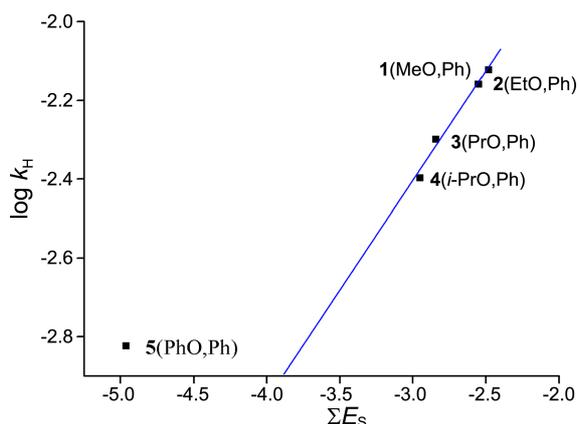
X	$k_{\text{H}} \times 10^3$	$k_{\text{D}} \times 10^3$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	42.4 ± 0.1	42.7 ± 0.3	0.993 ± 0.007
4-Me	13.4 ± 0.3	14.0 ± 0.1	0.957 ± 0.022
3-Me	6.58 ± 0.01	7.11 ± 0.01	0.926 ± 0.002
H	4.00 ± 0.01	4.68 ± 0.01	0.855 ± 0.003
3-MeO	2.01 ± 0.01	2.57 ± 0.01	0.782 ± 0.005
4-Cl	0.434 ± 0.001	1.32 ± 0.01	0.708 ± 0.005
3-Cl	0.344 ± 0.002	0.550 ± 0.001	0.625 ± 0.001
$\rho_{\text{X(H)}} = -3.12 \pm 0.08$		$\rho_{\text{X(D)}} = -2.79 \pm 0.09$	
$\beta_{\text{X(H)}} = 1.10 \pm 0.09$		$\beta_{\text{X(D)}} = 0.99 \pm 0.09$	

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

the direction of the consistent increase of the  $k_{\text{H}}/k_{\text{D}}$  value with X. For example, symbol of  $\uparrow$  indicates that the  $k_{\text{H}}/k_{\text{D}}$  value increases with a stronger nucleophile.

The observed sequence of the anilinolysis rates is **1** > **2** > **3** > **4** > **5**, giving the relative rates of 5.0(**1**) : 4.6(**2**) : 3.3(**3**) : 2.7(**4**) : 1(**5**). These results are not consistent with the expectations for the positive NBO charge at the reaction center P atom (**4** > **3** ≥ **2** > **1** > **5**), suggesting that the inductive effects of the two ligands do not play any role to decide the anilinolysis rates of Ph( $\text{R}_i\text{O}$ )P(=S)Cl-type phosphonochloridithioates. The sequence of the anilinolysis rates of **1** > **2** > **3** > **4** > **5** is inversely proportional to the size of the two ligands; 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 anilinolysis rates of the phosphonochloridithioates.

The Taft eq. of ' $\log k_{\text{H}} = \delta \Sigma E_{\text{S}} + C$ ' may be used to rationalize the steric effects of the two ligands on the reaction rate where  $k_{\text{H}}$  is the second-order rate constant with unsubstituted aniline in MeCN at 55.0 °C,  $E_{\text{S}}$  is the Taft steric constant [ $E_{\text{S}} = 0(\text{Me})$ ,  $-0.07(\text{Et})$ ,  $-0.36(\text{Pr})$ ,  $-0.47(\textit{i}\text{-Pr})$  and  $-2.48(\text{Ph})$ ],  $\Sigma E_{\text{S}}$  is the summation of the steric constants of the two ligands and  $\delta$  is the sensitivity coefficient.<sup>4</sup> It should be noted that the value of  $\Sigma E_{\text{S}}$  is not ' $E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i\text{O})$ ' but ' $E_{\text{S}}(\text{Ph}) + E_{\text{S}}(\text{R}_i)$ ' because the data of the Taft steric constant of  $\text{R}_i\text{O}$  are not available. Figure 1 shows the Taft plot of  $\log$



**Figure 1.** The Taft plot of  $\log k_H$  vs  $\Sigma E_s$  for the reactions of **1-5** with  $C_6H_5NH_2$  in MeCN at  $55.0\text{ }^\circ\text{C}$ . The number of the substrate and two ligands of  $R_1O$  and Ph are displayed next to the corresponding point.

$k_H$  with unsubstituted aniline ( $C_6H_5NH_2$ ) against the summation of Taft steric constants of the two ligands for the anilinolyses of five phosphonochloridothioates (**1-5**) in MeCN at  $55.0\text{ }^\circ\text{C}$ , giving the sensitivity coefficients of  $\delta = 0.56 \pm 0.02$  ( $r = 0.993$ ) with four substrates **1-4**.

The anilinolysis rate of **5** with phenoxy ligand shows positive deviation from the Taft plot. The anilinolysis rates of the chlorophosphates [( $R_1O$ )( $R_2O$ )P(=O)Cl-type]<sup>9</sup> and chlorothiophosphates [( $R_1O$ )( $R_2O$ )P(=S)Cl-type]<sup>9c,d,10</sup> show the same trends as those of the phosphonochloridothioates **1-5**. The dependences of  $\delta$  upon the two ligands of both chlorophosphate and chlorothiophosphate systems show quite similar trends, and both substrates with phenoxy ligand(s) show positive deviation from the Taft plots.<sup>9,10</sup> These indicate that the substrates with phenoxy ligand(s) of *a* group differ from those without phenoxy ligand(s) of *b* group regarding the steric effects of the two ligands on the anilinolysis rates. In other words, *a* and *b* group is different reaction series regarding the steric effects of the two ligands.

The second-order rate constant of the reaction of *Y-O*-aryl methyl phosphonochloridothioate [Me(YC<sub>6</sub>H<sub>4</sub>O)P(=S)Cl] with unsubstituted aniline in MeCN at  $55.0\text{ }^\circ\text{C}$  is  $k_H = 7.25 \times 10^{-3}\text{ M}^{-1}\text{ s}^{-1}$  and the NBO charge at the P atom is 1.432 when  $Y = H$ .<sup>11</sup> Comparing these values with  $k_H = 1.50 \times 10^{-3}\text{ M}^{-1}\text{ s}^{-1}$  and 1.462 of **5** [Ph(PhO)P(=S)Cl], the steric effects over the inductive effects of the two ligands are the major factor to determine the anilinolysis rate.

The size of PhS is more or less larger than that of PhO and, thus, the steric effects of the two ligands of **6** with Ph and PhS may be slightly greater than those of **5** with Ph and PhO in the TS. However, the anilinolysis rate of **6** is nine times slower than that of **5** which cannot be rationalized by the steric effects of the two ligands. The slower rate of **6** compared to that of **5** is attributed to the considerably smaller positive NBO charge at P atom of **6** compared to that of **5**, (NBO charge) =  $1.462(\mathbf{5}) - 0.999(\mathbf{6}) = 0.463$ . These can be supported by the following statements. It is well known that the P=O systems are more reactive than those of their P=S counterparts for several reasons, the so-called 'thio effect',

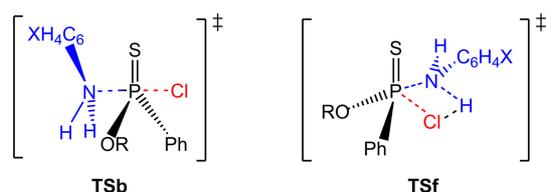
which is mainly the electronegativity difference between O and S, favors P=O over P=S systems.<sup>12</sup> For example, the anilinolysis rates of P=O systems (chlorophosphates) are 4-9 times faster than their P=S counterparts (chlorothiophosphates), and the differences of the NBO charges at the reaction center P atom between 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 counterpart)] are in the almost constant range of 0.54-0.57 in the gas phase.<sup>9,10</sup>

A concerted mechanism was proposed based on the negative  $\rho_{XY}$  [= -0.38(**5**) and -0.31(**6**)] values for the anilinolyses of **5** and **6**.<sup>13</sup> A concerted mechanism was also proposed for the anilinolysis of **2** based on the Brønsted coefficient [ $\beta_{X(H)} = 1.23(\mathbf{2})$ ]. In the present work, a concerted mechanism is proposed based on the Brønsted coefficient [ $\beta_{X(H)} = 1.26(\mathbf{1})$ ,  $1.04(\mathbf{3})$  and  $1.10(\mathbf{4})$ : comparable with  $\beta_{X(H)}(\mathbf{2}) = 1.23$ ,  $\beta_{X(H)}(\mathbf{5}) = 1.22-1.33$  and  $\beta_{X(H)}(\mathbf{6}) = 1.21-1.25$ ]. The relatively large Brønsted coefficients ( $\beta_{X(H)} = 1.04-1.33$ ) are typical for the anilinolyses of the phosphonochloridothioates even though the reactions proceed through a concerted  $S_N2$  mechanism.

The DKIEs have provided a useful means to determine the TS structures in the nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures. Incorporation of deuterium in the nucleophile has an advantage in that the  $\alpha$ -DKIEs reflect only the degree of bond formation. When partial deprotonation of the 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>14</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, since the N-H(D) vibrational frequencies invariably increase upon going to the TS because of an increase in steric congestion in the bond-making process.<sup>15</sup> The greater the degree of the steric congestion in the TS, the value of  $k_H/k_D$  becomes smaller.

The DKIEs of **1** ( $k_H/k_D = 1.08-1.17$ ) and **3** ( $k_H/k_D = 1.02-1.48$ ) are primary normal while those of **4** ( $k_H/k_D = 0.63-0.99$ ) and **6** ( $k_H/k_D = 0.65-0.98$ ) are secondary inverse. The DKIEs of **2** ( $k_H/k_D = 0.93-1.28$ ) and **5** ( $k_H/k_D = 0.44-1.34$ ) are both secondary inverse and primary normal. The  $k_H/k_D$  values of **1-3** and **5** increase as the aniline becomes less basic (symbol of  $\downarrow$ ), but those of **4** and **6** increase as the aniline becomes more basic (symbol of  $\uparrow$ ). The authors cannot find the consistent correlations between the  $\beta_X$  values and DKIEs, between the  $\beta_X$  values and variation trends of DKIEs, between the DKIEs and two ligands, or between the reaction mechanism and variation trends of DKIEs.

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



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

**Table 5.** Activation parameters for the reactions of **1-6** 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> Ph(MeO)P(=S)Cl	4.5	55	this work
<b>2:</b> Ph(EtO)P(=S)Cl	4.6	55	1
<b>3:</b> Ph(PrO)P(=S)Cl	4.7	55	this work
<b>4:</b> Ph( <i>i</i> -PrO)P(=S)Cl	5.1	54	this work
<b>5:</b> Ph(YC <sub>6</sub> H <sub>4</sub> O)P(=S)Cl	2.5-4.7	58-65	2
<b>6:</b> Ph(YC <sub>6</sub> H <sub>4</sub> S)P(=S)Cl	2.5-4.5	58-69	3

Thus, the authors propose the attacking direction of the anilines: for **1** and **3**, predominant frontside attack based on  $k_H/k_D = 1.08$ - $1.17$ (**1**) and  $1.02$ - $1.48$ (**3**); for **4** and **6**, predominant backside attack based on  $k_H/k_D = 0.63$ - $0.99$ (**4**) and  $0.65$ - $0.98$ (**6**); and finally for **2** and **5**, changing gradually from backside to frontside attack as the aniline becomes less basic based on  $k_H/k_D = 0.93$ - $1.28$ (**2**),  $0.44$ - $1.34$ (**5**) and variation trends with X, symbol of ↓.

Activation parameters, enthalpy and entropy of activation, are determined for the anilinolyses (with  $C_6H_5NH_2$ ) of **1**, **3** and **4** (Tables S1-S3; supporting information). The enthalpies of activation and entropies of activation of **1-6** are relatively low values ( $2.5$ - $5.1$  kcal mol<sup>-1</sup>) and large negative values ( $-54$  to  $-69$  cal mol<sup>-1</sup> K<sup>-1</sup>), respectively, as shown in Table 5. The relatively low value of activation enthalpy and large negative value of activation entropy are typical for the aminolyses of P=S systems.

## Experimental Section

**Materials.** HPLC grade MeCN (water content is less than 0.005%) was used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use. Deuterated anilines were synthesized by heating anilines and deuterium oxide (99.9 atom % D) and one drop of HCl as catalyst at 90 °C for 72 h, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by <sup>1</sup>H NMR. The substrates **1**, **3** and **4** were prepared by one step synthetic route. For **1**, phenyl thiophosphonic dichloride was added dropwise to methanol over 10 min. After stirring for 40 min in ice-water, the reaction mixture was extracted using distilled water/ethyl acetate. The organic extract was dried over anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and a yellow liquid product was isolated through column chromatography [silica gel, hexane/ethyl acetate (55:1)]. For **3**, phenyl thiophosphonic dichloride was

reacted with 1-propanol at  $-10.0$  °C with constant stirring. The product mixture was dried under reduced pressure and the product was isolated through column chromatography (30% ethyl acetate + *n*-hexane). For **4**, phenyl thiophosphonic dichloride was reacted with isopropanol at  $-5.0$  °C with constant stirring. The product mixture was dried under reduced pressure and the product was isolated through column chromatography (1% ethyl acetate + *n*-hexane). Analytical and spectroscopic data of the substrates of **1**, **3** and **4** gave the following results (supporting information):

**(C<sub>6</sub>H<sub>5</sub>)(CH<sub>3</sub>O)P(=S)Cl:** Yellow liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.75 (d,  $J = 12.0$  Hz, 3H), 7.44-7.92 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 53.15, 128.27, 128.50, 130.54, 131.05, 132.38, 133.23; <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ 96.41 (1P, P=S); MS (EI)  $m/z$ , 206 (M<sup>+</sup>).

**(C<sub>6</sub>H<sub>5</sub>)(PrO)P(=S)Cl:** Colorless liquid; <sup>1</sup>H-NMR (400 MHz, MeCN-*d*<sub>3</sub>) δ 0.98-1.01 (m, 3H), 1.77-1.82 (m, 2H), 4.26-4.36 (m, 2H), 7.58-8.06 (m, 5H); <sup>13</sup>C-NMR (100 MHz, MeCN-*d*<sub>3</sub>) δ 10.49, 23.99, 70.44, 129.88, 130.04, 131.16, 131.29, 134.64, 134.67; <sup>31</sup>P-NMR (162 MHz, MeCN-*d*<sub>3</sub>) δ 98.89 (1P, P=S); GC-MS (EI,  $m/z$ ) 234 (M<sup>+</sup>).

**(C<sub>6</sub>H<sub>5</sub>)(*i*-PrO)P(=S)Cl:** Colorless liquid; <sup>1</sup>H-NMR (400 MHz, MeCN-*d*<sub>3</sub>) δ 1.38 (d,  $J = 6.0$  Hz, 3H), 1.48 (d,  $J = 6.0$  Hz, 3H), 5.17-5.20 (m, 1H), 7.58-8.05 (m, 5H); <sup>13</sup>C-NMR (100 MHz, MeCN-*d*<sub>3</sub>) δ 23.64, 75.56, 129.54, 129.70, 130.75, 130.88, 134.19, 134.23; <sup>31</sup>P-NMR (162 MHz, MeCN-*d*<sub>3</sub>) δ 96.43 (1P, P=S); GC-MS (EI,  $m/z$ ) 234 (M<sup>+</sup>).

**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 anilines: [**1**] =  $1 \times 10^{-3}$  M and [X-aniline] = (0.03-0.15) M; [**3**] = [**4**] =  $5 \times 10^{-3}$  M and [X-Aniline] = (0.10-0.30) M. The  $k_{obsd}$  values were the average of at least three runs, which were reproducible within ± 3%.

**Product Analysis.** The substrates **1**, **3** and **4** were reacted with excess aniline for more than 15 half-lives at 55.0 °C in MeCN. The aniline hydrochloride salt was separated by filtration. Solvent was removed under reduced pressure. The product was isolated with ether by a work-up process and dried over anhydrous MgSO<sub>4</sub>. After filtration the product was isolated by evaporating the solvent under reduced pressure. The analytical and spectroscopic data of the product gave the following results (supporting information):

**(C<sub>6</sub>H<sub>5</sub>)(CH<sub>3</sub>O)P(=S)NHC<sub>6</sub>H<sub>5</sub>:** Brown liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.73 (d,  $J = 20.0$  Hz, 3H), 5.04 (1H, NH), 6.88-7.92(m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 53.08, 103.56, 117.51, 121.78, 128.25, 128.48, 128.63, 129.32, 131.04, 131.35, 131.87, 132.38, 132.66; <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ 67.35 (1P, P=S); MS (EI)  $m/z$ , 263 (M<sup>+</sup>).

**(C<sub>6</sub>H<sub>5</sub>)(PrO)P(=S)NHC<sub>6</sub>H<sub>5</sub>:** Liquid; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub> & TMS) δ 0.86-0.90 (m, 3H), 1.21-1.22 (m, 2H), 3.37-3.49 (m, 2H), 3.91-3.98 (m, br., 1H), 6.58-7.78 (m, 10H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub> & TMS) δ 15.82, 21.41, 65.49, 114.26, 115.45, 118.83, 125.62, 128.14, 128.90, 129.43,

144.92 (aromatic, 12C); <sup>31</sup>P-NMR (162 MHz, CDCl<sub>3</sub> & TMS) δ 74.02 (1P, P=S); GC-MS (EI, *m/z*) 291 (M<sup>+</sup>).

(C<sub>6</sub>H<sub>5</sub>)(*i*-PrO)P(=S)NHC<sub>6</sub>H<sub>5</sub>: Liquid; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub> & TMS) δ 1.25 (d, *J* = 6.0 Hz, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 5.09-5.12 (m, 1H), 5.67 (br. 1H, NH), 6.75-7.84 (m, 10H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub> & TMS) δ 26.20, 57.81, 108.35, 119.60, 128.91, 129.81, 134.81; <sup>31</sup>P-NMR (162 MHz, CDCl<sub>3</sub> & TMS) δ 71.77 (1P, P=S); GC-MS (EI, *m/z*) 291 (M<sup>+</sup>).

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