

## Kinetics and Mechanism of the Anilinolysis of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide in Acetonitrile<sup>†</sup>

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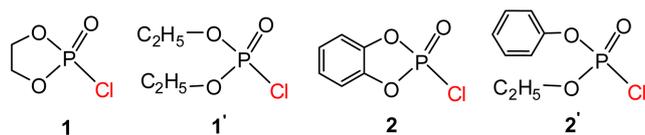
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The nucleophilic substitution reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with substituted anilines (XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>) and deuterated anilines (XC<sub>6</sub>H<sub>4</sub>ND<sub>2</sub>) are investigated kinetically in acetonitrile at 5.0 °C. The anilinolysis rate of **3** involving a cyclic five-membered ring is considerably fast because of small negative value of the entropy of activation ( $\Delta S^\ddagger = -2 \text{ cal mol}^{-1} \text{ K}^{-1}$ ) over considerably unfavorable enthalpy of activation ( $\Delta H^\ddagger = 18.0 \text{ kcal mol}^{-1}$ ). Great enthalpy and small negative entropy of activation are ascribed to sterically congested transition state (TS) and bulk solvent structure breaking in the TS. A concerted S<sub>N</sub>2 mechanism with a backside nucleophilic attack is proposed on the basis of the secondary inverse deuterium kinetic isotope effects,  $k_{\text{H}}/k_{\text{D}} < 1$ .

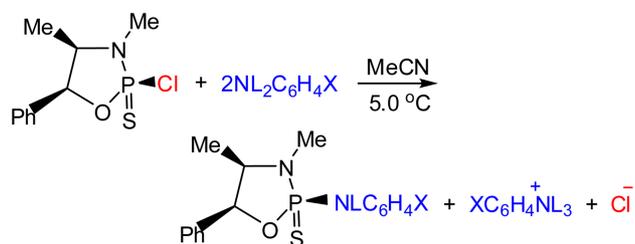
**Key Words** : Phosphoryl transfer reaction, Anilinolysis, (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide, Deuterium kinetic isotope effect

### Introduction

The anilinolysis rates of cyclic five-membered ring phosphate esters are much faster than their acyclic counterparts in acetonitrile (MeCN).<sup>1</sup> The anilinolysis rate of a cyclic five-membered ring of ethylene phosphorochloridate (**1**)<sup>1a</sup> is  $4.17 \times 10^3$  times faster than its acyclic counterpart of diethyl chlorophosphate (**1'**),<sup>1b</sup> and that of 1,2-phenylene phosphorochloridate (**2**)<sup>1c</sup> is  $1.53 \times 10^5$  times faster than its acyclic counterpart of phenyl ethyl chlorophosphate (**2'**)<sup>1d</sup> in MeCN at 55.0 °C.<sup>2</sup>



Continuing the kinetic study of the anilinolysis of a cyclic five-membered ring, the nucleophilic substitution reactions



L = H or D  
 X = 4-MeO, 4-Me, 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl

**Scheme 1.** The anilinolysis of (2*R*,4*R*,5*S*)-(+)-2-chloro-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) in MeCN.

of (2*R*,4*R*,5*S*)-(+)-2-chloro-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with substituted 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>) are investigated kinetically in MeCN at 5.0 ± 0.1 °C (Scheme 1), following after the previous work of the anilinolyses of ethylene (**1**) and 1,2-phenylene (**2**) phosphorochloridate in MeCN. The aim of the present work is to gain further information into the thiophosphoryl transfer reactions, as well as to compare with the reaction mechanism and deuterium kinetic isotope effects (DKIEs;  $k_{\text{H}}/k_{\text{D}}$ ) on the anilinolyses of cyclic five-membered rings of ethylene (**1**) and 1,2-phenylene (**2**) phosphorochloridate.

### Results and Discussion

The reactions were carried out under pseudo-first-order condition with a large excess of aniline. The pseudo-first-order rate constants observed ( $k_{\text{obsd}}$ ) for all the reactions followed Eq. (1) with negligible  $k_0$  ( $\approx 0$ ) in MeCN. The second-order rate constants, ( $k_{\text{H(D)}}$ ) were determined using Eq. (1) with at least five aniline concentrations, [XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>)]. No third-order or higher-order terms were detected, and no complications arising from side reaction were found in the determination of  $k_{\text{obsd}}$  and in the linear plots of Eq. (1). This suggests that the overall reaction follows cleanly the route given by Scheme 1.

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

The  $k_{\text{H}}$  and  $k_{\text{D}}$  values are summarized in Table 1, together with the DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) and the Hammett  $\rho_{\text{X}}$  and Brønsted  $\beta_{\text{X}}$  selectivity parameters. The  $\beta_{\text{X}}$  values were determined using  $\text{p}K_{\text{a}}$  values in water; the slopes from the plots of  $\log k_2(\text{MeCN})$  against  $\text{p}K_{\text{a}}(\text{H}_2\text{O})$ . Justification of this procedure has been experimentally and theoretically provided.<sup>6</sup> The values of  $\text{p}K_{\text{a}}(\text{X})$  and substituent constant ( $\sigma_{\text{X}}$ ) of the deute-

<sup>†</sup>This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

**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</sup> and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide (**3**) with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>) in MeCN at 5.0 °C

X	$k_{\text{H}} \times 10^3$	$k_{\text{D}} \times 10^3$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	184 ± 1 <sup>b</sup>	284 ± 1	0.648 ± 0.004 <sup>g</sup>
4-Me	81.8 ± 0.4	106 ± 1	0.772 ± 0.008
3-Me	33.7 ± 0.1	42.6 ± 0.1	0.791 ± 0.003
H	17.7 ± 0.1	21.9 ± 0.2	0.808 ± 0.009
4-F	8.68 ± 0.01	10.4 ± 0.1	0.835 ± 0.008
3-MeO	5.89 ± 0.04	6.56 ± 0.01	0.898 ± 0.006
4-Cl	2.28 ± 0.02	2.47 ± 0.02	0.923 ± 0.011
3-Cl	0.642 ± 0.003	0.654 ± 0.005	0.982 ± 0.009
$-\rho_{\text{X}}$	3.87 ± 0.03 <sup>c</sup>	4.13 ± 0.03 <sup>e</sup>	
$\beta_{\text{X}}$	1.37 ± 0.10 <sup>d</sup>	1.46 ± 0.10 <sup>f</sup>	

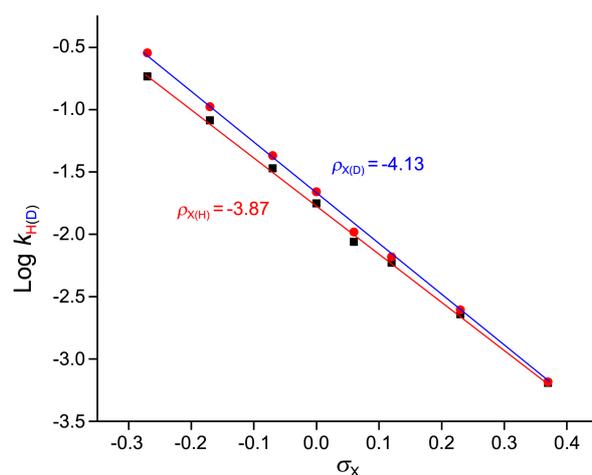
<sup>a</sup>The  $\sigma_{\text{X}}$  values were taken from ref. 3. The  $\text{p}K_{\text{a}}(\text{X})$  values of X-anilines in water were taken from ref. 4. <sup>b</sup>Standard deviation. <sup>c</sup>Correlation coefficient,  $r = 0.999$ . <sup>d</sup> $r = 0.994$ . <sup>e</sup> $r = 0.999$ . <sup>f</sup> $r = 0.994$ . <sup>g</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. 5.

rated X-anilines are assumed to be identical to those of the X-anilines. Perrin and coworkers reported that the basicities of  $\beta$ -deuterated analogs of benzylamine, *N,N*-dimethylaniline and methylamine increase roughly by 0.02  $\text{p}K_{\text{a}}$  units per deuterium, and that these effects are additive.<sup>7</sup> Thus, the  $\text{p}K_{\text{a}}(\text{X})$  values of deuterated X-anilines may be slightly greater than those of X-anilines, however, the difference is too small to be taken into account. Figures 1 and 2 show the Hammett ( $\log k_{\text{H(D)}} \text{ vs } \sigma_{\text{X}}$ ) and Brönsted [ $\log k_{\text{H(D)}} \text{ vs } \text{p}K_{\text{a}}(\text{X})$ ] plots, respectively, for substituent X variations in the nucleophiles. The substituent effects in the nucleophiles on the rates are in accord with those for a typical nucleophilic substitution reaction, that is, a stronger nucleophile results in a faster rate. The magnitudes of the  $\rho_{\text{X(H)}} (= -3.87)$  and  $\beta_{\text{X(H)}} (= 1.37)$  values with anilines are somewhat smaller than those ( $\rho_{\text{X(D)}} = -4.13$  and  $\beta_{\text{X(D)}} = 1.46$ ) with deuterated anilines, suggesting more sensitive to substituent effects of the deuterated anilines compared to those of anilines. The observed DKIEs are secondary inverse ( $k_{\text{H}}/k_{\text{D}} < 1$ ) and the  $k_{\text{H}}/k_{\text{D}}$  values invariably increase as the anilines become weaker, e.g., from  $k_{\text{H}}/k_{\text{D}} = 0.65$  with X = 4-MeO, via 0.81 with X = H, to 0.98 with 3-Cl.

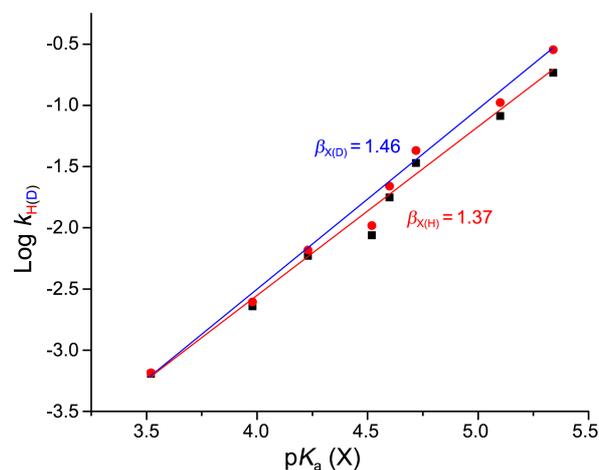
**Table 2.** Summary of Second-Order Rate Constants ( $k_{\text{H}} \times 10^3/\text{M}^{-1} \text{s}^{-1}$ ) with C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub> at 5.0 and 55.0 °C, Brönsted Coefficients ( $\beta_{\text{X(H)}}$ ), and DKIEs ( $k_{\text{H}}/k_{\text{D}}$ ) of the Reactions of **1-3** with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>) in MeCN

Substrate	$k_{\text{H}}(5.0 \text{ } ^\circ\text{C})^a$	$k_{\text{H}}(55.0 \text{ } ^\circ\text{C})^d$	$\beta_{\text{X(H)}}$	$k_{\text{H}}/k_{\text{D}}$	Trend
<b>1:</b> cC <sub>2</sub> H <sub>4</sub> O <sub>2</sub> P(=O)Cl	$4.56 \times 10^{-3b}$	$1.18 \times 10^{1e}$	1.56 <sup>g</sup> /0.79 <sup>h</sup>	0.87-1.20	↓
<b>2:</b> C <sub>6</sub> H <sub>4</sub> O <sub>2</sub> P(=O)Cl	$6.02 \times 10^{0c}$	$3.06 \times 10^{2c}$	1.54 <sup>g</sup> /0.35 <sup>h</sup>	0.88-1.94	↓
<b>3:</b> PhCHOCH(Me)N(Me)P(=S)Cl	$1.77 \times 10^{-2}$	$3.43 \times 10^{0f}$	1.46	0.65-0.98	↓

<sup>a</sup>The values with unsubstituted aniline at 5.0 °C. <sup>b</sup>Empirical kinetic data. <sup>c</sup>The values of  $k_{\text{H}} = 6.02 \times 10^0$  at 5.0 °C and  $3.06 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$  at 55.0 °C are calculated by extrapolation in the Arrhenius plot ( $r = 0.999$ ) with empirical kinetic data:  $k_{\text{H}} = 0.531$  (−20.0 °C), 0.863 (−15.0 °C), 1.53 (−10.0 °C), and  $2.46 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$  (−5.0 °C). See ref. 1c. <sup>d</sup>The values with unsubstituted aniline at 55.0 °C. <sup>e</sup>The value of  $k_{\text{H}} = 1.18 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$  at 55.0 °C is calculated by extrapolation in the Arrhenius plot ( $r = 0.999$ ) with empirical kinetic data:  $k_{\text{H}} = 0.671$  (−5.0 °C), 4.56 (5.0 °C), 11.1 (10.0 °C), and  $26.6 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  (15.0 °C). See ref. 1a. <sup>f</sup>The value of  $k_{\text{H}} = 3.43 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$  at 55.0 °C is calculated by extrapolation in the Arrhenius plot ( $r = 0.999$ ) with empirical kinetic data:  $k_{\text{H}} = 1.77$  (5.0 °C), 3.25 (10.0 °C), 5.45 (15.0 °C), and  $10.1 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$  (20.0 °C). <sup>g</sup>For X = (4-MeO, 4-Me, 3-Me). <sup>h</sup>X = (3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl).



**Figure 1.** The Hammett plots ( $\log k_{\text{H(D)}} \text{ vs } \sigma_{\text{X}}$ ) of the reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>) in MeCN at 5.0 °C.



**Figure 2.** The Brönsted plots [ $\log k_{\text{H(D)}} \text{ vs } \text{p}K_{\text{a}}(\text{X})$ ] of the reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>) in MeCN at 5.0 °C.

The second-order rate constants ( $k_{\text{H}}$ ) with unsubstituted aniline (C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>) at 5.0 and 55.0 °C, Brönsted coefficients ( $\beta_{\text{X(H)}}$ ), and  $k_{\text{H}}/k_{\text{D}}$  values of the reactions of **1-3** with XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>(D<sub>2</sub>) in MeCN are summarized in Table 2. It is well known that the P=S system is generally less reactive

than its P=O counterpart for several reasons, the so-called "thio effect", which is mainly the electronegativity difference between O and S, favoring O over S.<sup>8</sup> Although the P=S system of **3** is not its true P=O counterpart but its pseudo P=O counterpart of **1** (or **2**), the so-called "thio effect" is not working at low reaction temperature, e.g., 5.0 °C. The second-order rate constants for the anilinolysis of **1-3** give relative rates of 0.26(**1**):340(**2**):1(**3**) at 5.0 °C while 3.4(**1**):89(**2**):1(**3**) at 55.0 °C.<sup>9</sup> Note that the rate ratio of  $k_{\text{H}}(\mathbf{1})/k_{\text{H}}(\mathbf{3}) = 0.26$  at 5.0 °C in contrast to that of  $k_{\text{H}}(\mathbf{1})/k_{\text{H}}(\mathbf{3}) = 3.4$  at 55.0 °C since the activation energy of **1** ( $E_{\text{a}} = 28.3 \text{ kcal mol}^{-1}$ ) is considerably greater than that of **3** ( $E_{\text{a}} = 18.6 \text{ kcal mol}^{-1}$ ) and the Arrhenius plots of **1** and **3** have an isokinetic crossing point at 30.9 °C.<sup>10</sup> The free energy correlations for substituent X variations in the nucleophiles are linear with **3**, while **1** and **2** show biphasic concave upward free energy correlations with a break point at X = 3-Me. The values of  $\beta_{\text{X(H)}}$  with more basic anilines are greater than those with less basic anilines for both **1** and **2**. The  $\beta_{\text{X(H)}} (= 1.46)$  value of **3** is comparable to those of **1** ( $\beta_{\text{X(H)}} = 1.56$ ) and **2** ( $\beta_{\text{X(H)}} = 1.54$ ) with more basic anilines. The DKIEs of **3** are secondary inverse ( $k_{\text{H}}/k_{\text{D}} = 0.65\text{--}0.98 < 1$ ), while those of **1** and **2** are secondary inverse with more basic anilines and primary normal with less basic anilines:  $k_{\text{H}}/k_{\text{D}}(\mathbf{1}) = 0.87\text{--}0.99$  and  $1.12\text{--}1.20$ , and  $k_{\text{H}}/k_{\text{D}}(\mathbf{2}) = 0.88\text{--}1.00$  and  $1.19\text{--}1.94$  with more and less basic anilines, respectively.<sup>1a,c</sup>

In general, the predominant factor to determine the anilinolysis rate of acyclic substrate is the steric effects over the inductive effects (or the positive charge at the reaction center P atom) of the two ligands.<sup>11</sup> However, the rate ratios of cyclic substrates and their acyclic counterparts are huge:  $k_{\text{H}}(\mathbf{1})/k_{\text{H}}(\mathbf{1}') = 4.17 \times 10^3$  and  $k_{\text{H}}(\mathbf{2})/k_{\text{H}}(\mathbf{2}') = 1.53 \times 10^5$  at 55.0 °C. These results show that the anilinolysis rates of cyclic substrates are much faster ( $10^3\text{--}10^5$ ) than those of their acyclic counterparts and suggest that the major factor to determine the anilinolysis rate of cyclic substrates is different from that of their acyclic counterparts. The enthalpies and entropies of activation for the anilinolysis of **1**, **2**, **3**, **1'**, and **2'** at 55.0 °C are summarized in Table 3. At a glance, the enthalpies and entropies of activation of acyclic substrates are much smaller than those of cyclic substrates. Furthermore, the entropies of activation of cyclic substrates are large positive or small negative values. The anilinolysis rate of **1** involving a cyclic five-membered ring is four thousand times faster than its acyclic counterpart (**1'**) due to great

positive value of the entropy of activation of **1** ( $\Delta S^{\ddagger} = +30 \text{ eu}$ ) compared to large negative value of **1'** ( $\Delta S^{\ddagger} = -45 \text{ eu}$ ) over considerably unfavorable enthalpy of activation of **1** ( $\Delta H^{\ddagger} = 27.7 \text{ kcal mol}^{-1}$ ) compared to **1'** ( $\Delta H^{\ddagger} = 8.3 \text{ kcal mol}^{-1}$ ). The same trend is found for the anilinolysis of **2** and **2'**. The anilinolysis rate of **2** is one hundred fifty thousand times faster than its acyclic counterpart (**2'**) due to small negative value of the entropy of activation of **2** ( $\Delta S^{\ddagger} = -7 \text{ eu}$ ) compared to large negative value of **1'** ( $\Delta S^{\ddagger} = -51 \text{ eu}$ ) over unfavorable enthalpy of activation of **2** ( $\Delta H^{\ddagger} = 13.3 \text{ kcal mol}^{-1}$ ) compared to **2'** ( $\Delta H^{\ddagger} = 6.8 \text{ kcal mol}^{-1}$ ). This indicates that the much faster anilinolysis rates of cyclic substrates of **1** and **2** than their acyclic counterparts of **1'** and **2'** are ascribed to favorable entropy of activation term over unfavorable enthalpy of activation term. In the present work, the very fast anilinolysis rate is also predominantly due to the entropy of activation term ( $\Delta S^{\ddagger} = -2 \text{ eu}$ ) over unfavorable enthalpy of activation term ( $\Delta H^{\ddagger} = 18.0 \text{ kcal mol}^{-1}$ ).

Winstein and Fainberg studied the  $\text{S}_{\text{N}}1$  solvolyses of 2-chloro-2-methylpropane in six solvents (ethanol, acetic acid, methanol, formamide, formic acid, and water) at 25 °C, and found unusual large positive  $\Delta S^{\ddagger} (= +12 \text{ eu})$  value for the reaction in water, while negative  $\Delta S^{\ddagger} (= -2 \text{ to } -4 \text{ eu};$  relatively constant *ca.*  $-3 \text{ eu}$ ) values in the first five solvents.<sup>12</sup> As the solvent is changed from ethanol to water, the rate of solvolysis dramatically increases by a factor of  $3.35 \times 10^5$ . Moreover, the rate ratio of  $k(\text{formamide})/k(\text{water}) = 1.29 \times 10^{-3}$  is not substantiated by the normal solvent effect,<sup>13</sup> completely contrary to expectation for the Hughes-Ingold rule,<sup>14</sup> since the solvent polarity of formamide (dielectric constant  $\epsilon_{\text{r}} = 109.5$ ) is greater than that of water ( $\epsilon = 78.4$ ). The unusual fast solvolysis rate in water was rationalized by the highly ordered water structure breaking, resulting in the large positive  $\Delta S^{\ddagger} (= +12 \text{ eu})$  value and huge entropy of activation effect on the rate.<sup>12</sup> The authors reported that the five-membered rings are not in an apical-equatorial position but an equatorial position in the transition state (TS).<sup>15</sup> Accordingly, the steric congestion between cyclic five-membered ring and aniline nucleophile becomes much greater in the TS, resulting in greater value of the enthalpy of activation. The anilinolysis is the bimolecular reaction, in which the two molecules of reactants in the ground state (GS) become one activated complex in the TS. In general, the large negative value of entropy of activation is obtained for the bimolecular nucleophilic substitution reaction as seen in the anilinolysis of **1'** and **2'**. Thus, great positive (or very small negative) values of the entropies of activation of the anilinolyses suggest that the enormous degree of bulk solvent structure breaking occurs in the TS. This indicates that the degree of the ordered acetonitrile structure breaking is serious enough to give large positive entropy of activation, accompanying large enthalpy of activation, in the TS.

The DKIEs are one of the strong tools to clarify the reaction 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.

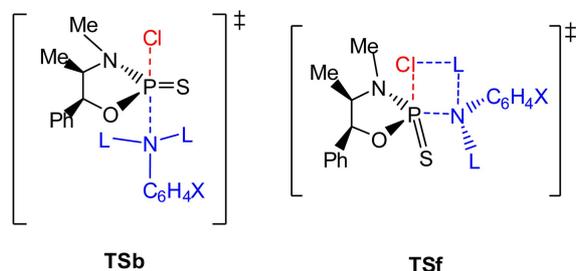
**Table 3.** Enthalpies and Entropies of Activation<sup>a</sup> for the Anilinolyses of **1**, **2**, **3**, **1'**, and **2'**

Substrate	$\Delta H^{\ddagger}$ /kcal mol <sup>-1</sup>	$\Delta S^{\ddagger}$ /cal mol <sup>-1</sup> K <sup>-1</sup>
<b>1</b> : $\text{cC}_2\text{H}_4\text{O}_2\text{P(=O)Cl}$	27.7	+30
<b>2</b> : $\text{C}_6\text{H}_4\text{O}_2\text{P(=O)Cl}$	13.3	-7
<b>3</b> : $\text{PhCHOCH(Me)N(Me)P(=S)Cl}$	18.0	-2
<b>1'</b> : $(\text{EtO})_2\text{P(=O)Cl}$	8.3	-45
<b>2'</b> : $(\text{EtO})(\text{PhO})\text{P(=O)Cl}$	6.8	-51

<sup>a</sup>The values of enthalpy and entropy of activation are at 55.0 °C.

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  $k_{\text{H}}/k_{\text{D}}$  values are greater than unity, primary normal ( $k_{\text{H}}/k_{\text{D}} > 1.0$ ).<sup>16</sup> The greater the extent of the hydrogen bond, the value of  $k_{\text{H}}/k_{\text{D}}$  becomes greater. In contrast, the DKIEs can only be secondary inverse ( $k_{\text{H}}/k_{\text{D}} < 1.0$ ) in a normal  $\text{S}_{\text{N}}2$  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>17</sup> The greater the degree of the steric congestion in the TS, the value of  $k_{\text{H}}/k_{\text{D}}$  becomes smaller.

The DKIEs of **1** and **2** change from secondary inverse ( $k_{\text{H}}/k_{\text{D}} = 0.87$ - $0.99$  with **1** and  $k_{\text{H}}/k_{\text{D}} = 0.88$ - $1.00$  with **2**) with the strongly basic anilines to primary normal ( $k_{\text{H}}/k_{\text{D}} = 1.12$ - $1.20$  with **1** and  $k_{\text{H}}/k_{\text{D}} = 1.19$ - $1.94$  with **2**) with the weakly basic anilines. In general, the magnitude of  $\beta_{\text{X}}$  value represents the degree of bond formation, and the greater  $\beta_{\text{X}}$  value is treated as greater degree of bond formation. As seen in Table 2, however, there is no correlation between the magnitudes of  $\beta_{\text{X}}$  and  $k_{\text{H}}/k_{\text{D}}$  values. The attacking direction of aniline nucleophile can be *semi*-quantitatively divided into three groups on the basis of the magnitudes of the  $k_{\text{H}}/k_{\text{D}}$  values: (i) predominant backside attack TSb when  $k_{\text{H}}/k_{\text{D}} < 1$ ; (ii) the fraction of the frontside attack TSf is greater than that of backside attack TSb when  $1.0 < k_{\text{H}}/k_{\text{D}} < 1.1$ ; (iii) predominant frontside attack TSf when  $k_{\text{H}}/k_{\text{D}} > 1.1$ . In the anilinolysis of **1** and **2**, thus, the backside nucleophilic attack TSb was proposed with the strongly basic anilines (X = 4-MeO, 4-Me, 3-Me) based on the secondary inverse DKIEs and frontside nucleophilic attack with a hydrogen-bonded, four-center type TSf was proposed with the weakly basic anilines (X = H, 4-F, 3-MeO, 4-Cl, 3-Cl) based on the primary normal DKIEs in which the reaction mechanism is a concerted  $\text{S}_{\text{N}}2$  pathway. In the present work of **3**, a concerted mechanism with a backside nucleophilic attack TSb is proposed on the basis of the secondary inverse DKIEs,  $k_{\text{H}}/k_{\text{D}} = 0.65$ - $0.98$  (Scheme 2).



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

### Experimental Section

**Materials.** (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide, commercially available, was used without further purification. HPLC grade

acetonitrile (water content is less than 0.005%) was used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described.<sup>1</sup> 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 hr, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by <sup>1</sup>H NMR.

**Kinetic Procedure.** Rates were measured conductometrically as previously described.<sup>1</sup> The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. Pseudo-first-order rate constants,  $k_{\text{obsd}}$  were measured by curve fitting analysis in origin program with a large excess of anilines, [substrate] =  $5 \times 10^{-4}$  M and [X-aniline] = (0.1-0.3) M. Second-order rate constants,  $k_{\text{H(D)}}$ , were obtained from the slope of a plot of  $k_{\text{obsd}}$  vs [X-aniline] with at least five concentrations of anilines. The  $k_{\text{obsd}}$  values were at least average of three runs, which were reproducible within  $\pm 3\%$ .

**Product Analysis.** 2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide was reacted with excess aniline for more than 15 half-lives at 5.0 °C in MeCN. The aniline hydrochloride salt was separated by filtration. Acetonitrile was removed under reduced pressure. The products was isolated through column chromatography (30% ethyl acetate/*n*-hexane) after treatment with ether and dilute HCl, then dried under reduced pressure. The analytical data are summarized as follows (see supplementary materials):

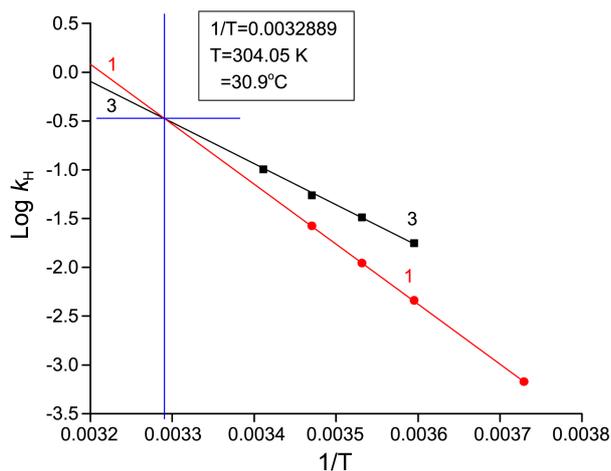
( $\text{C}_{10}\text{H}_{13}\text{NO}$ )P(=S)NHC<sub>6</sub>H<sub>5</sub>. Orange gummy gel; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub> & TMS)  $\delta$  0.88-0.89 (aliphatic, 3H, m), 2.86-2.94 (aliphatic, 3H, m), 3.47-3.48 (aliphatic, 1H, m), 3.79-3.87 (aliphatic, 1H, m), 5.38 (aliphatic, 1H, s), 5.82-5.84 (aliphatic, 1H, m) 6.94-7.42 (aromatic, 9H, m); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub> & TMS)  $\delta$  12.08 (aliphatic, 1C, s), 29.37 (aliphatic, 1C, s), 60.85 (aliphatic, 2C, d,  $J = 10.6$  Hz), 118.39-140.40 (aromatic, 12C, m); <sup>31</sup>P-NMR (162 MHz, CDCl<sub>3</sub> & TMS)  $\delta$  80.60 (1P, s, P=S); LC-MS (EI, *m/z*) 318 ( $\text{M}^+$ ).

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### References and Notes

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**Figure R1.** The Arrhenius plots of the anilinolysis of **1** and **3** in MeCN.