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Kinetics and Mechanism of the Anilinolysis of 1,2-Phenylene Phosphorochloridate in Acetonitrile

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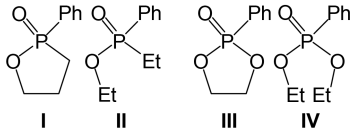
The nucleophilic substitution reactions of 1,2-phenylene phosphorochloridate (**1**) with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are investigated kinetically in acetonitrile at –15.0 °C. The studied substrate of 1,2-phenylene phosphorochloridate is cyclic five-membered ring of phosphorus ester, and the anilinolysis rate of **1** is much faster than its acyclic analogue (**4**: ethyl phenyl chlorophosphate) because of extremely small magnitude of the entropy of activation of **1** compared to **4**. The Hammett and Brönsted plots exhibit biphasic concave upwards for substituent X variations in the nucleophiles with a break point at X = 3-Me. The values of deuterium kinetic isotope effects (DKIEs; k_H/k_D) change from secondary inverse ($k_H/k_D < 1$) with the strongly basic anilines to primary normal ($k_H/k_D > 1$) with the weakly basic anilines. The secondary inverse with the strongly basic anilines and primary normal DKIEs with the weakly basic anilines are rationalized by the transition state (TS) variation from a predominant backside attack to a predominant frontside attack, in which the reaction mechanism is a concerted S_N2 pathway. The primary normal DKIEs are substantiated by a hydrogen bonded, four-center-type TS.

Key Words : Phosphoryl transfer reaction, Anilinolysis, 1,2-Phenylene phosphorochloridate, Biphasic concave upward free energy correlation, Deuterium kinetic isotope effect

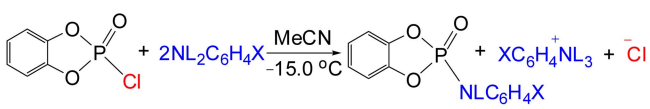
Introduction

The experimental (anilinolysis,[1] pyridinolysis,[2] and benzylaminolysis[3]) and theoretical[4] studies on the phosphoryl and thiophosphoryl transfer reactions have been carried out extensively by this lab. The studied substrates were all acyclic compounds and the leaving groups were mainly chloride, and sometimes phenoxide, thiophenoxide, isothiocyanate, and anilinide. The present work is the first kinetic investigation of the anilinolysis of phosphorus ester involving cyclic five-membered ring by this lab. It is known that cyclic five-membered ring phosphinate (and phosphate) esters in Scheme 1 are strained and they hydrolyze thousands (and millions) times faster than their acyclic analogues.[5] For example, the rate of base catalyzed hydrolysis of cyclic five-membered ring of 2-oxo-2-phenyl-1,2-oxaphospholane (**I**) is 6.2×10^3 times faster than its acyclic analogue of ethyl ethyl(phenyl)phosphinate (**II**), and that of cyclic five-membered ring of 2-oxo-2-phenyl-1,3,2-dioxaphospholane (**III**) is 1.5×10^6 times faster than its acyclic analogue of diethyl phenylphosphonate (**IV**).[6] The activation free energy differences of $\delta\Delta G^{\neq}$(**I** → **II**) = $\Delta G^{\neq}$(**II**) – $\Delta G^{\neq}$(**I**) = 5.2 kcal/mol and $\delta\Delta G^{\neq}$(**III** → **IV**) = $\Delta G^{\neq}$(**IV**) – $\Delta G^{\neq}$(**III**) = 8.4 kcal/mol are obtained. Assuming that the ring strain effects of **I** and **III** on the hydrolysis rate is the same, the difference of $\delta(\delta\Delta G^{\neq}) = 8.4[\delta\Delta G^{\neq}$(**III** → **IV**)] – $5.2[\delta\Delta G^{\neq}$(**I** → **II**)] = 3.2 kcal/mol is ascribed to a stereoelectronic effect of an additional oxygen atom to the five-membered ring, i.e., **III** has two oxygen atoms while **I** has one oxygen atom in the five-membered ring.[6]

In the present work, the nucleophilic substitution reactions of 1,2-phenylene phosphorochloridate (**1**), a cyclic five-membered ring phosphorus ester, with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are investigated kinetically in acetonitrile at –15.0 ± 0.1 °C (Scheme 2). The goal of this work is to gain further information into the phosphoryl transfer reactions, especially for the effect of ground state destabilization due to the ring strain on the anilinolysis rate, as well as to compare with the reaction mechanism and deuterium kinetic isotope effects (DKIEs; k_H/k_D) on the anilinolyses of acyclic $(R_1O)(R_2O)$-P(=O)Cl-type substrates: dimethyl [**2**: $(MeO)_2P(=O)Cl$],[1g] diethyl [**3**: $(EtO)_2P(=O)Cl$],[1g] ethyl phenyl [**4**: (EtO)(PhO)-P(=O)Cl],[1f] and diphenyl [**5**: $(PhO)_2P(=O)Cl$][1a] chlorophosphates. Herein, substrates of **1** and **4** can be treated as a pair of cyclic and acyclic analogues. The numbering of the



Scheme 1. Substrates of phosphorus esters with cyclic five-membered ring (**I** and **III**) and their acyclic analogues (**II** and **IV**).



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

Scheme 2. The studied reaction system.

substrates of **2-5** follows the sequence of the size of the two ligands, R_1O and R_2O.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq. (1) for all of the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The k_0 values were negligible ($k_0 = 0$) in MeCN. The second-order rate constants ($k_{H(D)}$) 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 2.

$$k_{obsd} = k_0 + k_{H(D)}[XC_6H_4NH_2(D_2)] \quad (1)$$

The k_H and k_D values are summarized in Table 1, together with the DKIEs (k_H/k_D) and the Hammett ρ_X and Brönsted β_X selectivity parameters. The pK_a(X) values of the X-anilines in water were used to obtain the Brönsted β_X values in MeCN, and this procedure was justified experimentally and theoretically.[7] The values of pK_a(X) and σ_X of the deuterated X-anilines are assumed to be identical to those of the X-anilines. The pK_a(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.[8] Figures 1 and 2 show the Hammett (log $k_{H(D)}$ *vs* σ_X) and Brönsted [log $k_{H(D)}$ *vs* pK_a(X)] plots, respectively, for substituent X variations in the nucleophiles. The stronger nucleophile leads to the faster rate as observed in a typical nucleophilic substitution reaction. However, both the Hammett and Brönsted plots exhibit biphasic concave upward free energy correlations for substituent X variations in the nucleophiles

Table 1. The Second-Order Rate Constants ($k_{H(D)} \times 10^0/M^{-1}\ s^{-1}$), Selectivity Parameters (ρ_X and β_X),[a] and DKIEs (k_H/k_D) of the Reactions of 1,2-Phenylene Phosphorochloridate (**1**) with $XC_6H_4NH_2(D_2)$ in MeCN at –15.0 °C

X	$k_H \times 10^0$	$k_D \times 10^0$	k_H/k_D
4-MeO	8.91 ± 0.08[b]	10.1 ± 0.1	0.882 ± 0.037[m]
4-Me	3.88 ± 0.04	4.14 ± 0.05	0.937 ± 0.030
3-Me	0.998 ± 0.008	1.00 ± 0.01	0.998 ± 0.013
H	0.863 ± 0.004	0.725 ± 0.007	1.19 ± 0.01
4-F	0.748 ± 0.006	0.573 ± 0.002	1.31 ± 0.01
3-MeO	0.660 ± 0.004	0.474 ± 0.003	1.39 ± 0.01
4-Cl	0.516 ± 0.004	0.328 ± 0.002	1.57 ± 0.01
3-Cl	0.361 ± 0.007	0.186 ± 0.001	1.94 ± 0.04
$-\rho_X$	4.75 ± 0.09[c,d]	5.02 ± 0.09[c,i]	
β_X	1.54 ± 0.01[c,e]	1.62 ± 0.01[c,j]	
$-\rho_X$	1.00 ± 0.01[f,g]	1.62 ± 0.02[f,k]	
β_X	0.35 ± 0.02[f,h]	0.57± 0.05[f,l]	

[a]The σ values were taken from ref. 9. The pK_a values of X-anilines in water were taken from ref. 10. [b]Standard deviation. [c]For X = 4-MeO, 4-Me, 3-Me. [d]Correlation coefficient, r = 0.991. [e]r = 0.999. [f]For X = 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl. [g]r = 0.999. [h]r = 0.993. [i]r = 0.992. [j]r = 1.000. [k]r = 0.999. [l]r = 0.987. [m]Standard error {= $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$} from ref. 11.

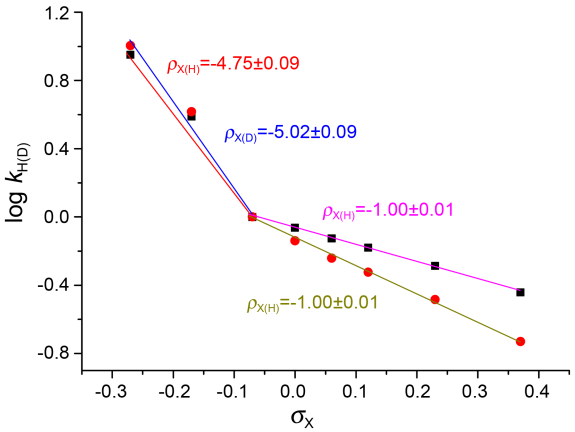


Figure 1. The Hammett plots (log $k_{H(D)}$ *vs* σ_X) of the reactions of 1,2-phenylene phosphorochloridate (**1**) with $XC_6H_4NH_2(D_2)$ in MeCN at –15.0 °C.

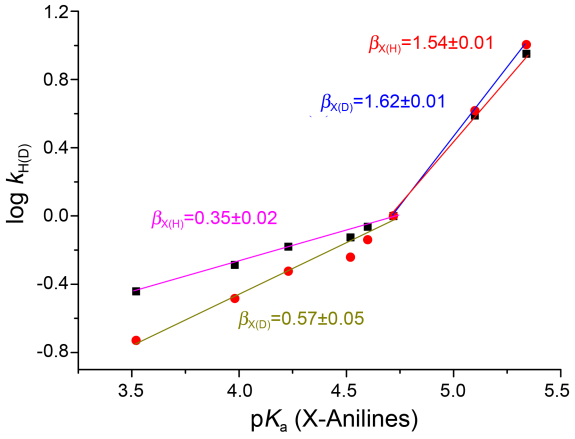


Figure 2. The Brönsted plots [log $k_{H(D)}$ *vs* pK_a(X)] of the reactions of 1,2-phenylene phosphorochloridate (**1**) with $XC_6H_4NH_2(D_2)$ in MeCN at –15.0 °C.

with a break point at X = 3-Me. The magnitudes of the $\rho_{X(H\ and\ D)}$ ($\rho_{X(H)}$ = –4.75 and $\rho_{X(D)}$ = –5.02) and $\beta_{X(H\ and\ D)}$ ($\beta_{X(H)}$ = 1.54 and $\beta_{X(D)}$ = 1.62) values with more basic anilines (X = 4-MeO, 4-Me, 3-Me) are much greater than those ($\rho_{X(H)}$ = –1.00, $\rho_{X(D)}$ = –1.62, $\beta_{X(H)}$ = 0.35, and $\beta_{X(D)}$ = 0.57) with less basic anilines (X = 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl). The magnitudes of the ρ_X and β_X values with the deuterated anilines are somewhat greater than those with the anilines, suggesting more sensitive to substituent effects of the deuterated anilines compared to anilines. The values of DKIEs (k_H/k_D) increase as the anilines become weaker: secondary inverse ($k_H/k_D < 1$) with the strongly basic anilines (X = 4-MeO, 4-Me, 3-Me) and primary normal ($k_H/k_D > 1$) with the weakly basic anilines (X = H, 4-F, 3-MeO, 4-Cl, 3-Cl).

The second-order rate constants (k_H) with unsubstituted aniline at 55.0 °C, summary of NBO charge at the reaction center P atom [B3LYP/6-311+G(d,p)][12] in the gas phase, Brönsted coefficients ($\beta_{X(H)}$ and $\beta_{X(D)}$), and k_H/k_D values of the reactions of **1**, **2**, **3**, **4**, and **5** with $XC_6H_4NH_2(D_2)$ in MeCN are summarized in Table 2. Solely considering the

Table 2. The Summary of Second-Order Rate Constants ($k_H \times 10^3/M^{-1}$ s^{-1}) with $C_6H_5NH_2$ at 55.0 °C, NBO Charge at the Reaction Center P Atom, Brönsted Coefficients ($\beta_{X(H)}$ and $\beta_{X(D)}$), and DKIEs (k_H/k_D) of the Reactions of **1**, **2**, **3**, **4**, and **5** with $XC_6H_4NH_2(D_2)$ in MeCN

Substrate	$k_H \times 10^3$[a]	Charge at P	$\beta_{X(H)}/\beta_{X(D)}$	k_H/k_D	Ref
1: $C_6H_4O_2P(=O)Cl$	306,000[b]	2.174	1.54;[c] 0.35[d]/1.62;[c] 0.57[d]	0.88-1.94[e]	this work
2: $(MeO)_2P(=O)Cl$	4.28	2.226	0.96/0.91[f]	0.80-0.98[f]	1g
3: $(EtO)_2P(=O)Cl$	2.82	2.236	1.06/0.99[f]	0.71-0.92[f]	1g
4: (EtO)(PhO)P(=O)Cl	2.00	2.233	1.13/1.23[f]	1.07-1.28[f]	1f
5: $(PhO)_2P(=O)Cl$	0.891	2.230	1.36/1.39[f]	0.61-0.87[f]	1a

[a]The values with unsubstituted aniline at 55.0 °C. [b]The value of $k_H = 306{,}000 \times 10^{-3}$ M^{-1} s^{-1} at 55.0 °C is calculated by extrapolation in the Arrhenius plot (r = 0.999) with empirical kinetic data: $k_H = 0.531$ (–20.0 °C), 0.863 (–15.0 °C), 1.53 (–10.0 °C), and 2.46×10^0 M^{-1} s^{-1} (–5.0 °C). See ref. 16. [c]For X = 4-MeO, 4-Me, 3-Me at –15.0 °C. [d]X = 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl at –15.0 °C. [e]The values at –15.0 °C. [f]The values at 55.0 °C.

positive charge of the reaction center P atom (or the inductive effects of the two ligands) in **1-5**, the sequence of the anilinolysis rates should be **1** < **2** < **5** < **4** < **3**. However, the observed sequence is **1** >> **2** > **3** > **4** > **5**, giving the rate ratio of 343,000(**1**) : 4.8(**2**)[1g] : 3.2(**3**)[1g] : 2.2(**4**)[1f] : 1(**5**).[1a] These results are not consistent with expectations for the positive charge at the reaction center P atom, strongly suggesting that the inductive effects of the two ligands do not play any role to decide the reactivity of anilinolysis of acyclic and cyclic $(R_1O)(R_2O)P(=O)Cl$-type substrates. Although the rate ratio is not great [k_H(**2**)/k_H(**5**) = 4.8], it is evident that the sequence of the anilinolysis rate of **2** > **3** > **4** > **5** is inversely proportional to the size of the two ligands; PhO,PhO(**5**) > EtO,PhO(**4**) > EtO,EtO(**3**) > MeO,MeO(**2**). The rate ratio indicates that the relative reactivities of acyclic $(R_1O)(R_2O)P(=O)Cl$-type substrates are predominantly dependent upon the steric effects over the inductive effects of the ligands.

The free energy correlations for substituent X variations in the nucleophiles are linear with **2-5**. However, **1** (the present work) shows biphasic concave upward free energy correlations with a break point. The anilinolysis of *O*-aryl methyl phosphonochloridothioates [**6**: Me(YPhO)P(=S)Cl] yielded biphasic concave downward free energy correlations for substituent X variations in the nucleophiles with a break region between X = H and 4-Cl.[1k] The authors have studied acyclic 21 $R_1R_2P(=O$ or S)Cl-type substrates where R_1 and R_2 are alkyl, alkoxy, phenyl, phenoxy, and/or thiophenoxy,[1a-l,n,o] and the anilinolysis of **6** only exhibited nonlinear free energy correlations among 21 $R_1R_2P(=O$ or S)Cl-type substrates. It is worthy of note that anilinolysis of **1** shows a break point while that of **6** showed a break region for substituent X variations in the nucleophiles, which suggest the anilinolysis mechanism of **1** and **6** is not the same for substituent X variations. The anilinolysis of **6** showed that the DKIEs are primary normal (k_H/k_D = 1.03-1.30) for stronger nucleophiles, and extremely large secondary inverse (k_H/k_D = 0.367-0.567) for weaker nucleophiles.[13] The cross-interaction constants (CICs)[14] are negative for stronger nucleophiles, while positive for weaker nucleophiles. The authors proposed the change of mechanism from a concerted process involving frontside nucleophilic attack for stronger nucleophiles to a stepwise process with a rate-limiting leaving group expulsion from the intermediate involving backside attack for weaker nucleophiles on the basis of the DKIEs and CICs.[1k]

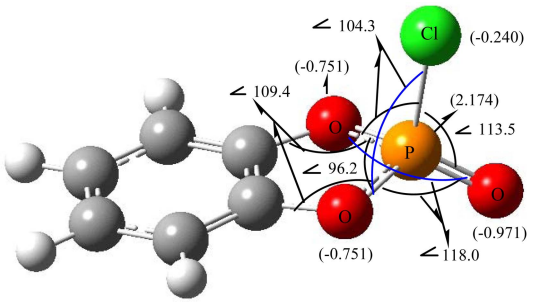


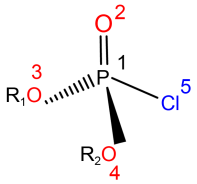
Figure 3. The B3LYP/6-311+G(d,p) geometry of **1** (1,2-phenylene phosphorochloridate) in the gas phase.

The B3LYP/6-311+G(d,p) geometry, bond angles, and natural bond order (NBO) charges of **1** in the gas phase are shown in Figure 3. The "Degree of distortion" ($\Delta\delta_{GS}$) of the ground state (GS) of substrate with tetracoordinated phosphorus from the regular tetrahedral structure is defined as eq. (2) by the authors.[1e,f,4b] The Σ means the sum of all six bond angles, θ_c is the calculated bond angle using the B3LYP/6-311+G(d,p) level, and θ_i is the ideal bond angle (109.5°) of the regular tetrahedral structure.

$$\Delta\delta_{GS} = \Sigma\,[|\theta_c - \theta_i|/\theta_i] = \Sigma\,|\theta_c - 109.5|/109.5 \qquad (2)$$

The bond angles and degree of distortion ($\Delta\delta_{GS}$) of **1-5** are summarized in Table 3. The MO theoretical structures of the substrates **1-5** show that the three oxygens and chlorine have more or less distorted tetrahedral geometry with the phosphorus atom at the center. The sequence of the degree of distortions is **1** > **5** > **4** > **3** ≈ **2**. In the case of **2-4**, the degree of distortion is proportional to the size of the two ligands: the greater the size of the two ligands, the greater degree of distortion is observed as expected. In the case of **1**, the smallest bond angle of ∠OPO (∠314) = 96.2° in cyclic five-membered ring is observed due to cyclic five-membered ring, resulting in the largest degree of distortion among **1-5**. Substrates of **1**, **2**, **3**, and **5** have the same two ligands, R_1O = R_2O, respectively. Only the substrate **1** has same bond angles, ∠213 = ∠214 and ∠315 = ∠415, i.e., having ClP=O symmetry plane. On the contrary, substrates **2**, **3**, and **5** do not have symmetry plane since ∠213 > ∠214 and ∠315 < ∠415, in spite of having the same two ligands, R_1O = R_2O.[15]

Table 3. Bond Angles and Degree of Distortion ($\Delta\delta_{GS}$) of **1-5** in the Gas Phase Calculated at the B3LYP/6-311+G(d,p) Level of Theory[a]



Substrate	∠213	∠214	∠215	∠314	∠315	∠415	$\Delta\delta_{GS}$
1: $C_6H_4O_2P(=O)Cl$	118.0	118.0	113.5	96.2	104.3	104.3	0.41
2: $(MeO)_2P(=O)Cl$	118.3	115.5	113.8	102.1	100.3	104.8	0.37
3: $(EtO)_2P(=O)Cl$	118.3	115.7	113.6	102.4	102.2	104.5	0.37
4: (EtO)(PhO)P(=O)Cl	118.1	116.0	114.1	101.2	100.9	104.3	0.38
5: $(PhO)_2P(=O)Cl$	118.5	116.7	113.9	100.7	99.8	104.8	0.40

[a]See ref. 1e for the substrates of **2-5**.

As seen in Table 2, the anilinolysis rate of cyclic five-membered ring of **1** is 1.53×10^5 times faster than its acyclic analogue of **4** in MeCN at 55.0 °C.[16-18] The difference of Gibbs free energy of activation, $\delta\Delta G^{\neq}(\mathbf{1} \rightarrow \mathbf{4}) = \Delta G^{\neq}(\mathbf{4}) - \Delta G^{\neq}(\mathbf{1}) = 7.8$ kcal/mol, is obtained of the anilinolysis of **1** and **4**.[16,18] The Gibbs free energy of activation ($\Delta G^{\neq}$) can be divided into the enthalpy of activation ($\Delta H^{\neq}$) and entropy of activation ($\Delta S^{\neq}$). (i) Regarding the enthalpy of activation term, the difference of $\delta\Delta H^{\neq}(\mathbf{1} \rightarrow \mathbf{4}) = \Delta H^{\neq}(\mathbf{4}) - \Delta H^{\neq}(\mathbf{1}) = -6.5$ kcal/mol indicates that the anilinolysis of **4** is rather more favorable than that of **1**. (ii) In contrast to the enthalpy of activation term, the entropy of activation term, the difference of $\delta\Delta S^{\neq}(\mathbf{1} \rightarrow \mathbf{4}) = \Delta S^{\neq}(\mathbf{4}) - \Delta S^{\neq}(\mathbf{1}) = -43.7$ cal mol^{-1} K^{-1}, equivalent to $-T\delta\Delta S^{\neq}(\mathbf{1} \rightarrow \mathbf{4}) = -328.15 \times (-43.7) \times 10^{-3} = +14.3$ kcal/mol at 55.0 °C, indicates that the anilinolysis of **1** is much more favorable than that of **4**. Thus, the much faster anilinolysis rate of **1** than **4** is not ascribed to the enthalpy of activation term but to the entropy of activation term, i.e., the much smaller negative entropy of activation term of **1** compared to **4** leads to much faster rate of **1** than **4** over the difference of the enthalpy of activation term. As mentioned earlier, base catalyzed hydrolysis rate of cyclic five-membered ring of **III** is 1.5×10^6 times faster than its acyclic analogue of **IV**, resulting in $\delta\Delta G^{\neq}(\mathbf{III} \rightarrow \mathbf{IV}) = \Delta G^{\neq}(\mathbf{IV}) - \Delta G^{\neq}(\mathbf{III}) = 8.4$ kcal/mol, and that of cyclic five-membered ring of **I** is 6.2×10^3 times faster than its acyclic analogue of **II**, resulting in $\delta\Delta G^{\neq}(\mathbf{I} \rightarrow \mathbf{II}) = \Delta G^{\neq}(\mathbf{II}) - \Delta G^{\neq}(\mathbf{I}) = 5.2$ kcal/mol.[6] As can be seen in Table 4, in contrast to the anilinolysis rates of **1** and **4**, the faster hydrolysis rates of cyclic substrates (**I** and **III**) compared to those of their acyclic counterparts (**II** and **IV**) are predominantly ascribed to the enthalpy of activation term. In other words, the faster anilinolysis rate of **1** is due to entropy controlled reaction while the faster hydrolysis rates of **I** and **III** are due to enthalpy controlled reactions.

The distinction between two systems, anilinolysis and hydrolysis, is the TS structure: (i) five-membered ring is intact in the TS for the anilinolysis; (ii) five-membered ring is partially broken in the TS for the hydrolysis, i.e., release of ring strain. This means that the main factor of the faster rate of cyclic substrate compared to its acyclic counterpart is different between the anilinolysis and hydrolysis. In the hydrolyses of **I** and **III**, the predominant factor of the faster rate is due to the ring strain of the reactant [ground state (GS) destabilization] and release of ring strain in the TS (TS stabilization), resulting in smaller magnitude of the enthalpy of activation compared to its acyclic analogue. In the present work, the magnitude of the entropy of activation (negative value) is considerably smaller compared to **4**, indicating that the TS structure of the anilinolysis of **1** is much less ordered compared to that of **4** accompanying much greater enthalpy of activation. The smaller entropy of activation and greater enthalpy of activation may be due to the greater degree of distortion of **1** compared to **4** in the GS.

The DKIEs are one of the strong tools to clarify the reaction mechanism. The DKIEs have provided a useful

Table 4. Activation Parameters and Differences of Activation Parameters[a] between Cyclic and their Acyclic Counterparts for the Anilinolysis of **1** and **4**, and Hydrolyses of **I**, **II**, **III**, and **IV**[a]

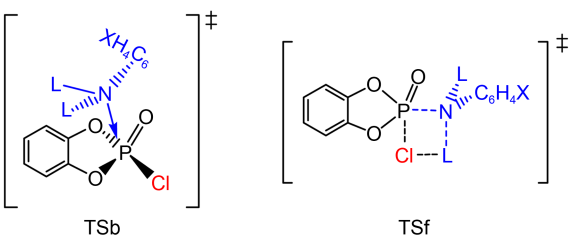
Substrate	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1}K^{-1}	$\Delta G^{\neq}$/kcal mol^{-1}	$\delta\Delta H^{\neq}$/kcal mol^{-1}	$-\delta\Delta S^{\neq}$/cal mol^{-1}K^{-1}	$-T\delta\Delta S^{\neq}$/kcal mol^{-1}	$\delta\Delta G^{\neq}$/kcal mol^{-1}
1: $C_6H_4O_2P(=O)Cl$	13.3	6.8	15.5	–6.5	43.7	14.3	7.8
4: (EtO)(PhO)P(=O)Cl	6.8	50.5	23.3				
I: $C_3H_6OP(=O)Ph$	4.2	45.4	17.7	7.3	–7.3	–2.1	5.2
II: Et(EtO)P(=O)Ph	11.5	38.1	22.9				
III: $C_2H_4O_2P(=O)Ph$	3.6	37.2	14.7	6.0	8.2	2.4	8.4
IV: $(EtO)_2P(=O)Ph$	9.6	45.4	23.1				

[a]The values of activation parameters of **1** and **2** are at 55.0 °C, and those of **I**, **II**, **III**, and **IV** are at 25.4 °C.

means to determine the TS structures in the nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures.[18] Incorporation of deuterium in the nucleophile has an advantage in that the α-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 ($k_H/k_D > 1.0$).[19] 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.[20] The greater the degree of the steric congestion in the TS, the value of k_H/k_D becomes smaller.

The DKIEs of **2** (k_H/k_D = 0.80-0.98),[1g] **3** (k_H/k_D = 0.71-0.92),[1g] and **5** (k_H/k_D = 0.61-0.87)[1a] are secondary inverse, while those of **4** (k_H/k_D = 1.07-1.28)[1f] are primary normal. In the present work (**1**), however, the DKIEs change from secondary inverse (k_H/k_D = 0.882-0.998; min with X = 4-MeO) with the strongly basic anilines to primary normal (k_H/k_D = 1.19-1.94; max with X = 3-Cl) with the weakly basic anilines.

In general, the magnitude of β_X value represents the degree of bond formation, and the greater β_X value is treated as greater degree of bond formation. As seen in Table 2, however, there is no correlation between the magnitudes of β_X and k_H/k_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_H/k_D values: (i) predominant backside attack TSb when $k_H/k_D < 1$; (ii) the fraction of the frontside attack TSf is greater than that of backside attack TSb when $1.0 < k_H/k_D < 1.1$: (iii) predominant frontside attack TSf when $k_H/k_D > 1.1$.[21] The authors accordingly proposed that the anilinolyses of **2**, **3**, and **5** proceed through a concerted mechanism involving predominant TSb on the basis of the secondary inverse DKIEs. On the contrary, a concerted mechanism involving predominant hydrogen-bonded, four-center-type TSf was proposed for the anilinolysis of **4** on the basis of the considerably large primary normal DKIEs. In the present work, thus, the backside nucleophilic attack TSb (Scheme 3) is proposed with the strongly basic anilines based on the secondary inverse DKIEs (k_H/k_D = 0.882-0.998) and frontside nucleophilic attack TSf (Scheme 3) is proposed with the weakly basic anilines based on the primary normal DKIEs (k_H/k_D = 1.19-1.94) in which the reaction mechanism is a concerted S_N2 pathway. The max value of k_H/k_D = 1.94 with X = 3-Cl in the present work is the second largest one after the max value of k_H/k_D = 2.10 of the anilinolysis of methyl phenyl phosphinic chloride [MePhP(=O)Cl] with X = 4-MeO.[1i]



Scheme 3. Backside attack TSb and frontside attack TSf.

Experimental Section

Materials. 1,2-Phenylene phosphorochloridate and HPLC-grade MeCN (water content is less than 0.005%) were used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use. Deuterated anilines were synthesized by heating anilines with deuterium oxide (99.9 atom % D) and one drop of HCl catalyst at 90 °C for 72 hours, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ^{1}H NMR.

Kinetics Measurement. Rates were measured conductometrically as previously described.[1] [Substrate] = 5×10^{-4} M and [Nucleophile] = 0.05-0.25 M were used for the present work. Pseudo-first-order rate constant values were the average of three runs that were reproducible within ± 3%.

Product Analysis. 1,2-Phenylene phosphorochloridate was reacted with excess 4-methoxyaniline, for more than 15 half-lives at –15.0 °C in MeCN. The 4-methoxy aniline hydrochloride salt was separated by filtration. Acetonitrile was removed under reduced pressure. The product was isolated by adding ether, chloroform and insoluble fraction was collected through filtration. Analytical and spectroscopic data of the product gave the following results:

[($C_6H_4O_2$)P(=O)NHC_6H_4(4-OCH_3)]. White crystal solid, mp (154-155) °C; ^{1}H-NMR (400 MHz, D_2O) δ 3.84-3.92 (aliphatic, 3H, m), 4.89 (aliphatic, 1H, s), 6.95-7.39 (8H, m, aromatic); ^{13}C-NMR (100 MHz, D_2O) δ 55.78 (aliphatic, 1C, s), 115.41-159.23 (aromatic, 12C, m); ^{31}P-NMR (162 MHz, D_2O) δ 22.84 (1P, s, P=O); *m/z*, 279 (M+).

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13. The DKIE of k_H/k_D = 0.367 for the reaction of *O*-4-cyanophenyl methyl phosphonochloridothioates with 4-chloroaniline in MeCN at 55.0 °C is the smallest value, i.e., unprecedented greatest secondary inverse.
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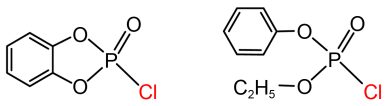
15. Although the two ligands are the same, $R_1O = R_2O$, there should be through space interaction between the two ligands, resulting in the absence of ClP=O symmetry plane. On the other hand, the two oxygens in cyclic five-membered ring of **1** are bonded to phenyl ring, resulting in the presence of ClP=O symmetry plane.
16. The second-order rate constants of the anilinolysis of **1** with unsubstituted anline ($C_6H_5NH_2$) in MeCN are measured as follows: k_H = 0.531 ± 0.003 (–20.0 °C), 0.863 ± 0.004 (–15.0 °C), 1.53 ± 0.01 (–10.0 °C), and 2.46 ± 0.01 × 10^0 M^{-1} s^{-1} (–5.0 °C). Gibbs free energy of activation of $\Delta G^{\neq}$ = 15.5 kcal mol^{-1}, enthalpy of activation of $\Delta H^{\neq}$ = 13.3 kcal mol^{-1}, and entropy of activation of $\Delta S^{\neq}$ = –6.8 cal mol^{-1} K^{-1} are obtained for the reaction of **1** with aniline ($C_6H_5NH_2$) in MeCN at 55.0 °C.
17. It may be reasonable that the acyclic counterpart of cyclic five-membered ring substrate of **1** is the substrate of **4**.



1 **4**

18. Gibbs free energy of activation of $\Delta G^{\neq}$ = 23.3 kcal mol^{-1}, enthalpy of activation of $\Delta H^{\neq}$ = 6.8 kcal mol^{-1}, and entropy of activation of $\Delta S^{\neq}$ = –50.5 cal mol^{-1} K^{-1} are obtained from $k_H \times 10^4/M^{-1}$ s^{-1} (*t* °C) = 13.8 (45.0°), 20.0 (55.0°), and 27.6 (65.0 °C) for the reaction of **4** with aniline ($C_6H_5NH_2$) in MeCN at 55.0 °C. See ref. 1f.
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21. This lab has cumulated data of DKIEs for the anilinolyses of various kinds of substrates in MeCN.