Kinetics and Mechanism of the Anilinolysis of Ethylene Phosphorochloridate in Acetonitrile

Hasi Rani Barai and Hai Whang Lee[*]

*Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr*

The nucleophilic substitution reactions of ethylene phosphorochloridate (**1c**) with substituted anilines (XC$_6$H$_4$NH$_2$) and deuterated anilines (XC$_6$H$_4$ND$_2$) are investigated kinetically in acetonitrile at 5.0 °C. The anilinolysis rate of **1c** involving a cyclic five-membered ring is four thousand times faster than its acyclic counterpart (**1a**: diethyl chlorophosphate) because of great *positive* value of the entropy of activation of **1c** ($\Delta S^{\neq}$ = +30 cal mol^{-1} K^{-1}) compared to negative value of **1a** ($\Delta S^{\neq}$ = –45 cal mol^{-1} K^{-1}) over considerably unfavorable enthalpy of activation of **1c** ($\Delta H^{\neq}$ = 27.7 kcal mol^{-1}) compared to **1a** ($\Delta H^{\neq}$ = 8.3 kcal mol^{-1}). Great enthalpy and positive entropy of activation are ascribed to sterically congested transition state (TS) and solvent structure breaking in the TS. The free energy correlations exhibit biphasic concave upwards for substituent X variations in the X-anilines with a break point at X = 3-Me. The deuterium kinetic isotope effects are secondary inverse (k_H/k_D < 1) with the strongly basic anilines and primary normal (k_H/k_D > 1) with the weakly basic anilines and rationalized by the TS variation from a dominant backside attack to a dominant frontside attack, respectively. A concerted S$_N$2 mechanism is proposed and the primary normal deuterium kinetic isotope effects are substantiated by a hydrogen bonded, four-center-type TS.

Key Words : Phosphoryl transfer reaction, Anilinolysis, Ethylene phosphorochloridate, Biphasic concave upward free energy correlation, Deuterium kinetic isotope effect

Introduction

It is known that a cyclic five-membered ring phosphate ester is strained and it hydrolyzes millions times faster than its acyclic counterpart.[1] The rate of base catalyzed hydrolysis of a cyclic five-membered ring of 2-oxo-2-phenyl-1,3,2-dioxaphospholane (**3c**) is 1.48×10^6 times faster than its acyclic counterpart of diethyl phenylphosphonate (**3a**) (Scheme 1).[2]

Continuing the kinetic study of the anilinolysis of phosphorus ester involving a cyclic five-membered ring, the nucleophilic substitution reactions of ethylene phosphorochloride (**1c**) with substituted anilines (XC$_6$H$_4$NH$_2$) and deuterated anilines (XC$_6$H$_4$ND$_2$) are investigated kinetically
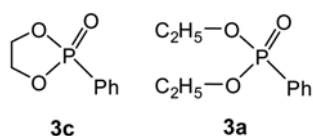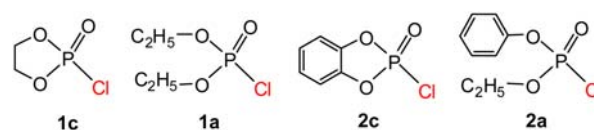

Scheme 1. Cyclic five-membered ring of 2-oxo-2-phenyl-1,3,2-dioxaphospholane (**3c**) and its acyclic counterpart of diethyl phenylphosphonate (**3a**).
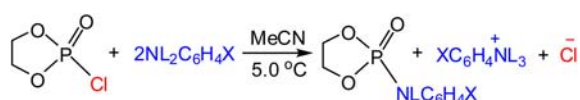
L = H or D
X = 4-MeO, 4-Me, 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl

Scheme 2. The studied reaction system.

Scheme 3. Cyclic five-membered rings of ethylene (**1c**) and 1,2-phenylene (**2c**) phosphorochloridate, and their acyclic counterparts of diethyl (**1a**) and phenyl ethyl (**2a**) chlorophosphate.

in acetonitrile (MeCN) at 5.0 ± 0.1 °C (Scheme 2), following after the previous work of the anilinolysis of 1,2-phenylene phosphorochloridate (**2c**) in MeCN at –15 °C.[3]

The aim of the present 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 the two pairs of cyclic and their acyclic counterparts (Scheme 3): ethylene phosphorochloridate (**1c**);[4] 1,2-phenylene phosphorochloridate (**2c**)[3] and phenyl ethyl chlorophosphate (**2a**).[5] Herein, *c* (cyclic) and *a* (acyclic) represent cyclic and acyclic substrate, respectively.

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_{obsd}) for all the reactions followed eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants, ($k_{H(D)}$) were determined using

eq. (1) with at least five aniline concentrations, $[XC_6H_4NH_2(D_2)]$. No third-order or higher-order terms were detected, and no complications arising from side reaction were found in the determination of k_{obsd} and in the linear plots of eq. (1). This suggests that the overall reaction follows cleanly the route given by Scheme 2.

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

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 β_X values were determined using pK_a values in water; the slopes from the plots of log $k_2(MeCN)$ against $pK_a(H_2O)$. Justification of this procedure has been experimentally and theoretically provided.[6] The values of $pK_a(X)$ and substituent constant (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.[7] 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 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. However, both the Hammett and Brönsted plots exhibit biphasic concave upward free energy correlations for substituent X variations in the nucleophiles with a break point at X = 3-Me, as observed for the anilinolysis of **2c**.[1] The magnitudes of the $\rho_{X(H \text{ and } D)}$ ($\rho_{X(H)} = -4.92$ and $\rho_{X(D)} = -5.20$) and $\beta_{X(H \text{ and } D)}$ ($\beta_{X(H)} = 1.56$ and $\beta_{X(D)} = 1.65$) values with more basic anilines (X = 4-MeO, 4-Me, 3-Me) are greater than those ($\rho_{X(H)} = -2.24$, $\rho_{X(D)} = -2.39$, $\beta_{X(H)} = 0.79$, and $\beta_{X(D)} = 0.84$)

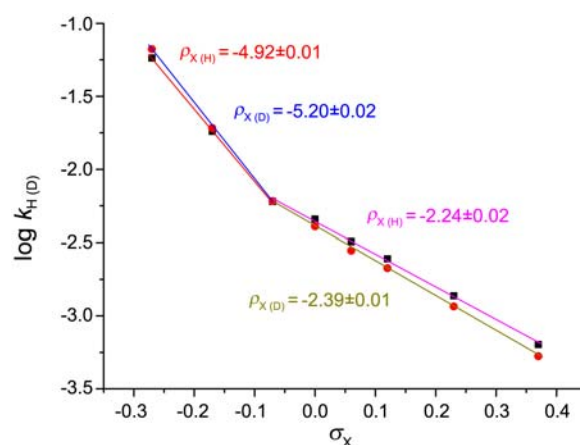**Figure 1.** The Hammett plots (log $k_{H(D)}$ *vs* σ_X) of the reactions of ethylene phosphorochloridate (**1c**) with $XC_6H_4NH_2(D_2)$ in MeCN at 5.0 °C.
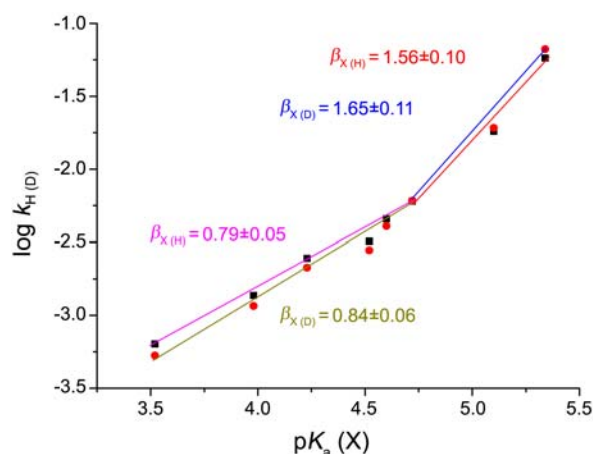
Figure 2. The Brönsted plots [log $k_{H(D)}$ *vs* $pK_a(X)$] of the reactions of ethylene phosphorochloridate (**1c**) with $XC_6H_4NH_2(D_2)$ in MeCN at 5.0 °C.

Table 1. Second-Order Rate Constants ($k_{H(D)} \times 10^3/M^{-1} s^{-1}$), Selectivity Parameters (ρ_X and β_X),[a] and DKIEs (k_H/k_D) of the Reactions of Ethylene Phosphorochloridate (**1c**) with $XC_6H_4NH_2(D_2)$ in MeCN at 5.0 °C

X	$k_H \times 10^3$	$k_D \times 10^3$	k_H/k_D
4-MeO	57.9 ± 0.1^b	66.5 ± 0.3	0.871 ± 0.004^m
4-Me	18.2 ± 0.2	19.1 ± 0.1	0.953 ± 0.004
3-Me	6.02 ± 0.02	6.06 ± 0.03	0.993 ± 0.006
H	4.56 ± 0.01	4.07 ± 0.02	1.12 ± 0.01
4-F	3.21 ± 0.01	2.79 ± 0.01	1.15 ± 0.01
3-MeO	2.46 ± 0.01	2.12 ± 0.02	1.16 ± 0.01
4-Cl	1.37 ± 0.01	1.16 ± 0.01	1.18 ± 0.01
3-Cl	0.635 ± 0.003	0.529 ± 0.003	1.20 ± 0.01
$-\rho_X$	$4.92 \pm 0.01^{c,d}$	$5.20 \pm 0.02^{c,i}$	
β_X	$1.56 \pm 0.10^{c,e}$	$1.65 \pm 0.11^{c,j}$	
$-\rho_X$	$2.24 \pm 0.02^{f,g}$	$2.39 \pm 0.01^{f,k}$	
β_X	$0.79 \pm 0.05^{f,h}$	$0.84 \pm 0.06^{f,l}$	

[a]The σ_X values were taken from ref. 8. The $pK_a(X)$ values of X-anilines in water were taken from ref. 9. [b]Standard deviation. [c]For X = (4-MeO, 4-Me, 3-Me). [d]Correlation coefficient, r = 0.999. [e]r = 0.990. [f]For X = (3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl). [g]r = 0.999. [h]r = 0.993. [i]r = 0.999. [j]r = 0.988. [k]r = 0.999. [l]r = 0.989. [m]Standard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ from ref. 10.

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 those of anilines. The values of DKIEs (k_H/k_D) increase as the anilines become weaker: secondary inverse ($k_H/k_D < 1$) with more basic anilines (X = 4-MeO, 4-Me, 3-Me) and primary normal ($k_H/k_D > 1$) with less basic anilines (X = 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl), as observed for the anilinolysis of **2c**.[1]

The second-order rate constants (k_H) with unsubstituted aniline ($C_6H_5NH_2$) at 55.0 °C, summary of natural bond order (NBO) charges at the reaction center P atom [B3LYP/6-311+G(d,p) level of theory][11] in the gas phase, Brönsted coefficients ($\beta_{X(H)}$ and $\beta_{X(D)}$), and the values of DKIEs (k_H/k_D) of the reactions of **1c**, **1a**, **2c**, and **2a** with $XC_6H_4NH_2(D_2)$ in MeCN are summarized in Table 2. The free energy correlations for substituent X variations in the nucleophiles are linear with acyclic substrates of **1a** and **2a**. On the contrary, cyclic substrates of **1c** and **2c** show biphasic

Table 2. 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 **1c**, **1a**, **2c**, and **2a** with $XC_6H_4NH_2(D_2)$ in MeCN

Substrate	$k_H \times 10^{3a}$	Charge at P	$\beta_{X(H)}/\beta_{X(D)}$	k_H/k_D	ref.
1c: $C_2H_4O_2P(=O)Cl$	$11{,}800^b$	2.196	$1.56,^d 0.79^e/1.65,^d 0.84^e$	0.87-1.20	this work
1a: $(EtO)_2P(=O)Cl$	2.82	2.236	1.06/0.99	0.71-0.92	4
2c: $C_6H_4O_2P(=O)Cl$	$306{,}000^c$	2.174	$1.54,^d 0.35^e/1.62,^d 0.57^e$	0.88-1.94	3
2a: $(EtO)(PhO)P(=O)Cl$	2.00	2.233	1.13/1.23	1.07-1.28	5

^{a}The values with unsubstituted aniline at 55.0 °C. ^{b}The value of $k_H = 11{,}800 \times 10^{-3}\,M^{-1}\,s^{-1}$ at 55.0 °C is calculated by extrapolation in the Arrhenius plot (r = 0.999) with empirical kinetic data: $k_H = 0.671$ (−5.0 °C), 4.56 (5.0 °C), 11.1 (10.0 °C), and $26.6 \times 10^{-3}\,M^{-1}\,s^{-1}$ (15.0 °C). See ref. 12. ^{c}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 $2.46 \times 10^0\,M^{-1}\,s^{-1}$ (−5.0 °C). See ref. 3. ^{d}For X = (4-MeO, 4-Me, 3-Me). ^{e}X = (3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl).

concave upward free energy correlations with a break point at X = 3-Me. The DKIEs of **1a** are secondary inverse (k_H/k_D = 0.71-0.92 < 1), while those of **2a** are primary normal (k_H/k_D = 1.07-1.28 > 1). The DKIEs of cyclic substrates of **1c** and **2c** are secondary inverse with more basic anilines and primary normal with less basic anilines: k_H/k_D(**1c**) = 0.871-0.993 and 1.12-1.20, and k_H/k_D(**2c**) = 0.882-0.998 and 1.19-1.94 with more and less basic anilines, respectively.

The rate ratio of acyclic substrates is k_H(**2a**)/k_H(**1a**) = 0.71, while that of cyclic substrates is k_H(**2c**)/k_H(**1c**) = 26. The rate ratios of cyclic substrates and their acyclic counterparts are great: k_H(**1c**)/k_H(**1a**) = 4.17 × 10³ and k_H(**2c**)/k_H(**2a**) = 1.53 × 10⁵. These results show that the anilinolysis rates of cyclic substrates are much faster (10³-10⁵) 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. 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.[4,5,13]

The activation parameters (enthalpy, entropy, and Gibbs free energy of activation) and the changes in the activation parameters from cyclic substrates to their acyclic counterparts for the anilinolysis of **1c**, **1a**,[4] **2c**,[3] and **2a**[5] at 55.0 °C, and hydrolyses of **3c**[2] and **3a**[2] at 25.4 °C are summarized in Table 3. The change in the Gibbs free energy of activation, $\delta\Delta G^{\neq}$(**1c**→**1a**) = $\Delta G^{\neq}$(**1a**) − $\Delta G^{\neq}$(**1c**) = 23.1-17.7 = 5.4 kcal/mol is obtained of the anilinolysis of **1c** and **1a**. The Gibbs free energy of activation difference ($\delta\Delta G^{\neq}$) can be divided into the enthalpy ($\delta\Delta H^{\neq}$) and entropy of activation difference ($\delta\Delta S^{\neq}$): (i) the enthalpy of activation difference, $\delta\Delta H^{\neq}$(**1c**→**1a**)

= $\Delta H^{\neq}$(**1a**) − $\Delta H^{\neq}$(**1c**) = 8.3-27.7 = −19.4 kcal mol^{-1}, indicates that the anilinolysis of **1a** is much more favorable than that of **1c**; (ii) in contrast to the enthalpy of activation difference, the entropy of activation difference, $\delta\Delta S^{\neq}$(**1c**→**1a**) = $\Delta S^{\neq}$(**1a**) − $\Delta S^{\neq}$(**1c**) = −45.1 − (+30.4) = −75.5 cal mol^{-1} K^{-1}, equivalent to −$T\delta\Delta S^{\neq}$(**1c**→**1a**) = −328.15 × (−75.5) × 10^{-3} = +24.8 kcal mol^{-1}, indicates that the anilinolysis of **1c** is much more favorable than that of **1a**. It is worthy of note that the enthalpy of activation of $\Delta H^{\neq}$(**1c**) = 27.7 kcal mol^{-1} is relatively great value and, moreover, entropy of activation of $\Delta S^{\neq}$(**1c**) = +30.4 cal mol^{-1} K^{-1} is unusually great *positive* value. The anilinolysis rate of **1c** involving a cyclic five-membered ring is four thousand times faster than its acyclic counterpart (**1a**) due to great *positive* value of the entropy of activation of **1c** compared to negative value of **1a** over considerably unfavorable enthalpy of activation of **1c** compared to **1a**. The same trend was found for the anilinolysis of **2c** and **2a**, as can be seen in Table 3.[3] The authors conclude that the faster anilinolysis rates of cyclic substrates of **1c** and **2c** than their acyclic counterparts of **1a** and **2a** are ascribed to favorable entropy of activation term over unfavorable enthalpy of activation term.

As mentioned earlier, base catalyzed hydrolysis rate of cyclic five-membered ring of **3c** is million times faster than its acyclic counterpart of **3a**, resulting in $\delta\Delta G^{\neq}$(**3c**→**3a**) = $\Delta G^{\neq}$(**3a**) − $\Delta G^{\neq}$(**3c**) = 8.4 kcal mol^{-1} at 25.4 °C. Regarding the enthalpy and entropy of activation, the faster hydrolysis rate of cyclic substrates (**3c**) compared to that of its acyclic counterpart (**3a**) is predominantly ascribed to the enthalpy of activation term of $\delta\Delta H^{\neq}$(**3c**→**3a**) = $\Delta H^{\neq}$(**3a**) − $\Delta H^{\neq}$(**3c**) = +6.0 kcal/mol in addition to minor positive contribution of the entropy of activation term of $\delta\Delta S^{\neq}$(**3c**→**3a**) = $\Delta S^{\neq}$(**3a**) −

Table 3. Activation Parameters^a and Changes in Activation Parameters from Cyclic Substrates to their Acyclic Counterparts for the Anilinolysis of **1c**, **1a**, **2c**, and **2a**, and Hydrolyses of **3c** and **3a**

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}
1c: $C_2H_4O_2P(=O)Cl$	27.7	+30.4	17.7	−19.4	−75.5	24.8	5.4
1a: $(EtO)_2P(=O)Cl^b$	8.3	−45.1	23.1				
2c: $C_6H_4O_2P(=O)Cl$	13.3	−6.8	15.5	−6.5	−43.7	14.3	7.8
2a: $(EtO)(PhO)P(=O)Cl$	6.8	−50.5	23.3				
3c: $C_2H_4O_2P(=O)Ph$	3.6	−37.2	14.7	6.0	−8.2	2.4	8.4
3a: $(EtO)_2P(=O)Ph$	9.6	−45.4	23.1				

^{a}The values of activation parameters of **1c**, **1a**,[4] **2c**,[1] and **2a**[5] are at 55.0 °C, and those of **3c**[2] and **3a**[2] are at 25.4 °C. ^{b}Ref. 14.
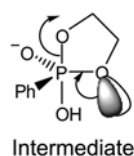
Scheme 4. TBP-5C intermediate of base catalyzed hydrolysis of **3c**.

$\Delta S^{\neq}(\mathbf{3c}) = -8.2$ cal mol^{-1} K^{-1}, equivalent to $-T\delta\Delta S^{\neq}(\mathbf{3c}\rightarrow\mathbf{3a})$ $= -298.55 \times (-8.2) \times 10^{-3} = +2.4$ kcal/mol. These results suggest that the reason of the faster anilinolysis rate of **1c** (and **2c**) compared to that of **1a** (and **2a**) is different from the reason of the faster hydrolysis of **3c** compared to that of **3a**. The Gibbs free energy of activation difference of 8.4 kcal mol^{-1} of base catalyzed hydrolysis of **3c** is thought to be derived from both a ring strain effect (~5.2 kcal mol^{-1}) and a stereoelectronic effect (~3.2 kcal mol^{-1}). The release of the ring strain is attributed to forming the trigonal bipyramidal pentacoordinate (TBP-5C) intermediate, resulting in spanning the five-membered ring in an apical-equatorial position (Scheme 4). The stereoelectronic effect is attributed to the two lone pairs on the basal ring oxygen oriented partially antiperiplanar to the apical ring ester bond leaving group, displayed with the arrows in Scheme 4.[1b,2]

The B3LYP/6-311+G(d,p) geometries, bond angles, and NBO charges of **1c** and **2c** in the gas phase are shown in Figure 3. The "Degree of distortion" ($\Delta\delta_{GS}$) of the ground state (GS) of substrate with tetracoordinate phosphorus from the regular tetrahedral structure is defined as Eq. (2) by the authors.[5,15] 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.

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

The bond angles and degree of distortion ($\Delta\delta_{GS}$) of **1c**, **1a**, **2c**, and **2a** are summarized in Table 4. The MO theoretical structures of the substrates **1c**, **1a**, **2c**, and **2a** show that the three oxygens and chlorine have somewhat distorted tetrahedral geometry with the phosphorus atom at the center. The sequence of the degree of distortions is **2c** > **1c** > **2a** > **1a**. At
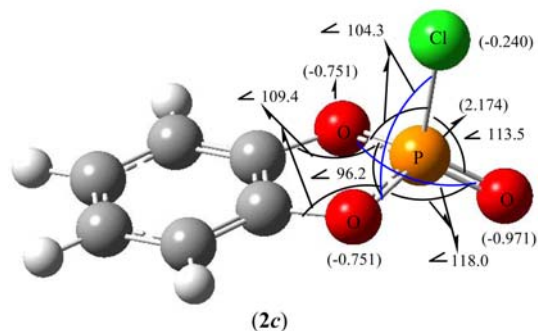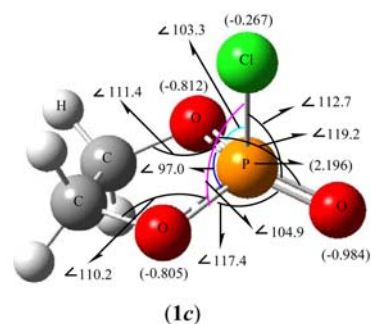

Figure 3. The B3LYP/6-311+G(d,p) geometry of ethylene (**1c**) and 1,2-phenylene (**2c**)[3] phosphorochloridate in the gas phase.

a glance, substrates of **1c**, **1a**, and **2c** have symmetry plane since they have the same two ligands, however, only the substrate of **2c** has ClP=O symmetry plane with same bond angles; ∠213 = ∠214 = 118.0°, and ∠315 = ∠415 = 104.3°. In the substrate of **2c**, the phenyl ring leads to ∠13C(carbon of position 1 in phenyl ring) = ∠14C(carbon of position 2 in phenyl ring) = 109.7° (Fig. 3), resulting in ClP=O symmetry plane.[16] In the substrate of **1c**, bond angles of ∠13C (= 111.4°) and ∠14C(= 110.2°) are not same (Fig. 3), resulting in the absence of ClP=O symmetry plane.[16] In the substrate of **1a**, although the two ligands are the same, EtO, there is through space interaction between the two ligands, resulting in the absence of ClP=O symmetry plane.

In the present work, much greater value of the enthalpy of activation of **1c** [$\Delta H^{\neq}(\mathbf{1c}) = 27.7$ kcal mol^{-1}] compared to that of **1a** [$\Delta H^{\neq}(\mathbf{1a}) = 8.3$ kcal mol^{-1}] implies that the

Table 4. Bond Angles and Degree of Distortions ($\Delta\delta_{GS}$) of **1c**, **1a**, **2c**, and **2a** Calculated at the B3LYP/6-311+G(d,p) Level of Theory in the Gas Phase
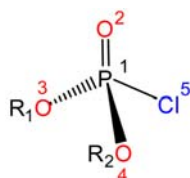
Substrate	∠213	∠214	∠215	∠314	∠315	∠415	$\Delta\delta_{GS}$
1c: C$_2$H$_4$O$_2$P(=O)Cl	117.4	119.2	112.7	97.0	103.3	104.9	0.40
1a: (EtO)$_2$P(=O)Cl[a]	118.3	115.7	113.6	102.4	102.2	104.5	0.37
2c: C$_6$H$_4$O$_2$P(=O)Cl[b]	118.0	118.0	113.5	96.2	104.3	104.3	0.41
2a: (EtO)(PhO)P(=O)Cl[c]	118.1	116.0	114.1	101.2	100.9	104.3	0.38

[a]Ref. 4 and 15. [b]Ref. 3. [c]Ref. 5 and 15.

absence of the release of the ring strain and stereoelectronic effect of the lone pairs of oxygen in the TS. The authors, thus, suggest that the five-membered ring is not in an apical-equatorial position, which has been observed in the base catalyzed hydrolysis of **3c** (see Scheme 4), but an equatorial position in the TS.[17] Accordingly, the steric congestion between cyclic five-membered ring and aniline nucleophile becomes greater in the TS, resulting in greater value of the enthalpy of activation. Great positive value of the entropy of activation $[\Delta S^{\neq}(\mathbf{1c}) = +30.4 \text{ cal mol}^{-1} \text{ K}^{-1}]$ implies that the TS structure is much less ordered compared to the GS structure. Taking into account the molecularity of two, great positive entropy of activation must be ascribed to enormous degree of solvent structure breaking in the TS.[18] Comparing **1c** with **2c**, the TS of **1c** is much more sterically congested (much greater enthalpy of activation) and much more solvent structure breaking (much greater entropy of activation) in the TS compared to that of **2c** in spite of the degree of distortion of **2c** is greater than that of **1c** in the GS.

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. 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 **1a** ($k_H/k_D = 0.71\text{-}0.92$)[4] are secondary inverse, while those of **2a** ($k_H/k_D = 1.07\text{-}1.28$)[5] are primary normal. The DKIEs of **1c** and **2c** change from secondary inverse ($k_H/k_D = 0.871\text{-}0.993$ with **1c** and $k_H/k_D = 0.882\text{-}0.998$ with $\mathbf{2c}^3$) with the strongly basic anilines to primary normal ($k_H/k_D = 1.12\text{-}1.20$ with **1c** and $k_H/k_D = 1.19\text{-}1.94$ with $\mathbf{2c}^3$) 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 anilinolysis of **1a** proceeds through a concerted mechanism involving predominant TSb on the basis of the
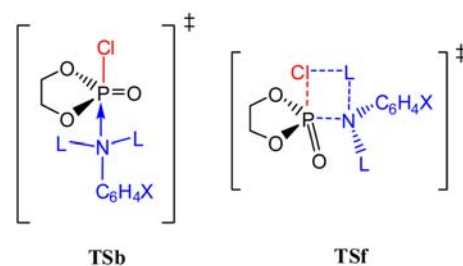
Scheme 5. Backside attack TSb and frontside attack TSf.

secondary inverse DKIEs.[4] On the contrary, a concerted mechanism involving predominant hydrogen-bonded, four-center-type TSf was proposed for the anilinolysis of **2a** on the basis of the considerably large primary normal DKIEs.[5] In the present work (**1c**), thus, the backside nucleophilic attack TSb (Scheme 5) is proposed with the strongly basic anilines (X = 4-MeO, 4-Me, 3-Me) based on the secondary inverse DKIEs ($k_H/k_D = 0.871\text{-}0.993$) and frontside nucleophilic attack TSf (Scheme 5) is proposed with the weakly basic anilines (X = H, 4-F, 3-MeO, 4-Cl, 3-Cl) based on the primary normal DKIEs ($k_H/k_D = 1.12\text{-}1.20$) in which the reaction mechanism is a concerted S_N2 pathway. The proposed mechanisms for the anilinolysis of **2c** were the same as those of **1c** since the trends of the DKIEs and free energy correlations with X are the same as **1c**.[3] The max value of $k_H/k_D = 1.94$ with X = 3-Cl of **2c** 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.[13d]

It should be noted that the real primary normal DKIE due to TSf is greater than the observed value, since the observed value is the sum of: (i) the primary normal DKIE ($k_H/k_D > 1$) because of the partial deprotonation of one of the two N–H(D) bonds, TSf; (ii) the secondary inverse DKIE ($k_H/k_D < 1$) because of the steric hindrance that increases the out-of-plane bending vibrational frequencies of the other N–H(D) bond; (iii) lowering of the k_H/k_D value because of the nonlinear and asymmetrical structure of N···H(D)···Cl; (iv) lowering of the k_H/k_D value because of the heavy atom (N and Cl) contribution of the reaction-coordinate motion.[22]

Experimental Section

Materials. Ethylene 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.

Kinetic Measurement. Rates were measured conductometrically as previously described.[3-5,13] [Substrate] = 5×10^{-4} M and [Nucleophile] = 0.10-0.30 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. Ethylene phosphorochloridate 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. Solvent of MeCN was removed under reduced pressure. The product was isolated through column chromatography (50% ethyl acetate/*n*-hexane) after treatment with ether and dilute HCl, and then dried under reduced pressure. The analytical data are summarized as follows:

[(C$_2$H$_4$O$_2$)P(=O)NHC$_6$H$_5$]. Fawn oily liquid; ^{1}H-NMR (400 MHz, CDCl$_3$ & TMS) δ 3.43-3.49 (aliphatic, 4H, m), 4.21 (aliphatic, 1H, s), 7.23-7.37 (aromatic, 5H, m); ^{13}C-NMR (100 MHz, CDCl$_3$ & TMS) δ 66.29-66.84 (aliphatic, 2C, m), 114.67-160.44 (aromatic, 6C, m); ^{31}P-NMR (162 MHz, CDCl$_3$ & TMS) δ −6.42 (1P, s, P=O); GC-MS (EI, *m/z*) 199 (M$^+$).

References and Notes

1. (a) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. (b) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047.
2. Yang, J. C.; Gorenstein, D. G. *Tetrahedron* **1987**, *43*, 479.
3. Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3355.
4. Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2008**, *21*, 544.
5. Hoque, M. E. U.; Dey, N. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2007**, *5*, 3944.
6. (a) Ritchie, C. D. in *Solute-Solvent Interactions*, Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Chapter 4. (b) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 54. (c) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099. (d) Oh, H. K.; Woo, S. Y.; Shin, C. H.; Park, Y. S.; Lee, I. *J. Org. Chem.* **1997**, *62*, 5780.
7. Perrin and coworkers reported that the basicities of *β*-deuterated analogs of benzylamine, *N,N*-dimethylaniline and methylamine increase roughly by 0.02 p*K*$_a$ units per deuterium, and that these effects are additive; (a) Perrin, C. I.; Engler, R. E. *J. Phys. Chem.* **1991**, *95*, 8431. (b) Perrin, C. I.; Ohta, B. K.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 15008. (c) Perrin, C. I.; Ohta, B. K.; Kuperman, J.; Liberman, J.; Erdelyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 9641.
8. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
9. Streitwieser, A., Jr.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*, 4th ed.; Macmillan: New York, 1992; p 735.
10. Crumpler, T. B.; Yoh, J. H. *Chemical Computations and Errors*; John Wiley: New York, 1940; p 178.
11. Hehre, W. J.; Random, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; Chapter 4.
12. The second-order rate constants of the anilinolysis of ethylene phosphorochloridate (**1c**) with unsubstituted anline (C$_6$H$_5$NH$_2$) in MeCN are measured as follows: k_H = 0.671 ± 0.025 (−5.0 °C), 4.56 ± 0.01 (5.0 °C), 11.1 ± 0.1 (10.0 °C), and 26.6 ± 0.1 × 10^{-3} M^{-1} s^{-1} (15.0 °C). Gibbs free energy of activation of $\Delta G^{\neq}$ = 17.7 kcal mol^{-1}, enthalpy of activation of $\Delta H^{\neq}$ = 27.7 ± 0.1 kcal mol^{-1}, and entropy of activation of ΔS = +30.4 ± 0.3 cal mol^{-1} K^{-1} are obtained for the reaction of **1c** with aniline (C$_6$H$_5$NH$_2$) in MeCN at 55.0 °C.
13. (a) Hoque, M. E. U.; Dey, S.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Org. Chem.* **2007**, *72*, 5493. (b) Hoque, M. E. U.;
Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 936. (c) Lumbiny, B. J.; Lee, H. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 2065. (d) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2009**, *22*, 425. (e) Dey, N. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2009**, *30*, 975. (f) Hoque, M. E. U.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2009**, *7*, 2919. (g) Dey, N. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2010**, *31*, 1403. (8) Dey, N. K.; Kim, C. K.; Lee, H. W. *Org. Biomol. Chem.* **2011**, *9*, 717. (h) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1939. (i) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1997. (j) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2306.
14. The second-order rate constants of the anilinolysis of diethyl chlorophosphate (**2a**) with unsubstituted aniline (C$_6$H$_5$NH$_2$) in MeCN are measured as follows: k_H = 1.88 (45.0 °C), 2.82 (55.0 °C), and 4.34 × 10^{-3} M^{-1} s^{-1} (65.0 °C). Gibbs free energy of activation of $\Delta G^{\neq}$ = 23.1 kcal mol^{-1}, enthalpy of activation of $\Delta H^{\neq}$ = 8.3 kcal mol^{-1}, and entropy of activation of $\Delta S^{\neq}$ = −45.1 cal mol^{-1} K^{-1} are obtained for the reaction of **2a** with aniline (C$_6$H$_5$NH$_2$) in MeCN at 55.0 °C.
15. Dey, N. K.; Han, I. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 2003.
16. Scheme shows the absence of the symmetry plane of **1c** and the presence of the symmetry plane of **2c**. Cl–P=O makes the present plane in Scheme.

1c   2c
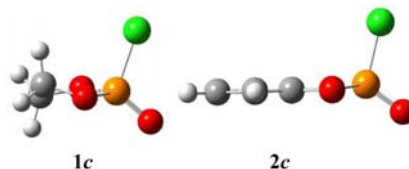
17. When the structure of the TS (or intermediate) assumes to be the TBP-5C for a backside nucleophilic attack, the leaving group for the anilinolysis of **1c** and P–O(oxygen in the five-membered ring) bond for the base catalyzed hydrolysis of **3c** should be in an apical position. The five-membered ring is in an apical-equatorial position since the P–O bond cleavage should occur in an apical position in the intermediate. On the contrary, the five-membered ring is in an equatorial position in the TS for the anilinolysis of **1c** since the leaving group Cl should be in an equatorial position in the TS.
18. The huge degree of solvent structure breaking overwhelms the increase of solvation (solvent structure making) due to the charge separation in the TS.
19. (a) Lee, I.; Koh, H. J.; Lee, B. S.; Lee, H. W. *J. Chem. Soc., Chem. Commun.* **1990**, 335. (b) Lee, I. *Chem. Soc. Rev.* **1995**, *24*, 223. (c) Marlier, J. F. *Acc. Chem. Res.* **2001**, *34*, 283. (d) Westaway, K. C. *Adv. Phys. Org. Chem.* **2006**, *41*, 217. (e) Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 736. (f) Gronert, S.; Fajin, A. E.; Wong, L. *J. Am. Chem. Soc.* **2007**, *129*, 5330.
20. (a) Poirier, R. A.; Youliang, W.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526. (b) Yamata, H.; Ando, T.; Nagase, S.; Hanamusa, M.; Morokuma, K. *J. Org. Chem.* **1984**, *49*, 631. (c) Xhao, X. G.; Tucker, S. C.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 826.
21. This lab has cumulated data of DKIEs for the anilinolyses of various kinds of substrates in MeCN.
22. (a) Melander, L., Jr.; Saunders, W. H. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980. (b) Kaldor, S. B.; Saunders, W. H., Jr. *J. Chem. Phys.* **1978**, *68*, 509. (c) Swain, C. C.; Pegues, E. E. *J. Am. Chem. Soc.* **1958**, *80*, 812. (d) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401. (e) Kwart, H.; Brechbid, M. W.; Acheson, R. M.; Ward, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 4671.