http://dx.doi.org/10.5012/bkcs.2012.33.1.270

Kinetics and Mechanism of the Pyridinolysis of 1,2-Phenylene 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*
Received November 8, 2011, Accepted November 21, 2011

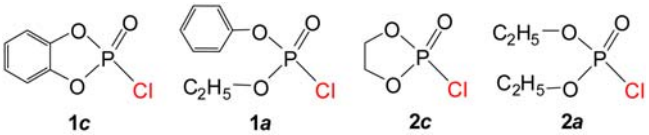
The nucleophilic substitution reactions of 1,2-phenylene phosphorochloridate (**1*c***) with X-pyridines are investigated kinetically in acetonitrile at –25.0 °C. The free energy correlations for substituent X variations in the nucleophiles exhibit biphasic concave upwards with a break point at X = 3-Ph. The pyridinolysis rate of **1*c*** with a cyclic five-membered ring is 2.70×10^5 times faster than its acyclic counterpart (**1*a***: phenyl ethyl chlorophosphate) because of great positive value of the entropy of activation of **1*c*** ($\Delta S^{\neq}$ = +26 eu) compared to negative value of **1*a*** ($\Delta S^{\neq}$ = –24 eu) over considerably unfavorable enthalpy of activation of **1*c*** ($\Delta H^{\neq}$ = 20.5 kcal mol^{-1}) compared to **1*a*** ($\Delta H^{\neq}$ = 12.7 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. A concerted mechanism involving a change of nucleophilic attacking direction from a frontside attack with the strongly basic pyridines to a backside attack with the weakly basic pyridines is proposed on the basis of greater selectivity parameters (ρ_X = –1.99 and β_X = 0.41) with the strongly basic pyridines compared to those (ρ_X = –0.42 and β_X = 0.07) with the weakly basic pyridines.

Key Words : Phosphoryl transfer reaction, Pyridinolysis, 1,2-Phenylene phosphorochloridate, Biphasic concave upward free energy correlation

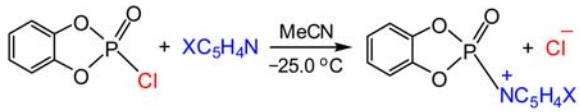
Introduction

In the previous work, the authors reported the pyridinolyses[1] and anilinolyses[2] of various kinds of substrates. The aminolyses rates of cyclic five-membered rings are exceptionally faster (10^3-10^5 times) than their acyclic counterparts in acetonitrile (MeCN). The pyridinolysis rate (with C_5H_5N) of a cyclic five-membered ring of ethylene phosphorochloridate (**2*c***)[1s] is 6.02×10^4 times faster than its acyclic counterpart of diethyl chlorophosphate (**2*a***)[1g] at 35.0 °C. The anilinolysis rate (with $C_6H_5NH_2$) of a cyclic five-membered ring of 1,2-phenylene phosphorochloridate (**1*c***)[2s] is 1.53×10^5 times faster than its acyclic counterpart of phenyl ethyl chlorophosphate (**1*a***),[2f] and that of a cyclic five-membered ring of ethylene phosphorochloridate (**2*c***)[2u] is 4.18×10^3 times faster than its acyclic counterpart of diethyl chlorophosphate (**2*a***)[2g] at 55.0 °C.[2g]

Continuing the kinetic study of the aminolysis of phosphorus ester involving a cyclic five-membered ring, the nucleophilic substitution reactions of 1,2-phenylene phosphorochloridate (**1*c***) with substituted pyridines (XC_5H_4N) are investigated kinetically in MeCN at –25.0 ± 0.1 °C (Scheme 2) to gain further information into the reactivity



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



X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN

Scheme 2. The pyridinolysis of 1,2-phenylene phosphorochloridate (**1*c***) in MeCN at –25.0 °C.

and mechanism of the aminolyses of cyclic five-membered ring substrates, as well as to compare the relevant aminolyses of their acyclic counterparts of phenyl ethyl [**1*a***: (EtO)(PhO)P(=O)Cl][1v,2f] and diethyl [**2*a***: $(EtO)_2P(=O)Cl$][1g,2g] chlorophosphates in MeCN. Herein, the notations of ***c*** and ***a*** of the substrates indicate a ***c***yclic five-membered and its ***a***cyclic counterpart, respectively.

Results and Discussion

The reactions were carried out under pseudo-first-order conditions with a large excess of pyridine. The observed pseudo-first-order rate constants (k_{obsd}) for all the reactions obeyed Eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants (k_{Pyr}) were determined with at least five pyridine concentrations. The linear plots of Eq. (1) suggest a lack of any base-catalysis or side reaction, and the overall reaction is described by Scheme 2.

$$k_{obsd} = k_0 + k_{Pyr}[XC_5H_4N] \quad (1)$$

The second-order rate constants [k_{Pyr} (M^{-1} s^{-1})] are summarized in Table 1. The rates are so fast that the reaction temperature is as low as –25.0 °C to obtain the rate constant.

Table 1. Second-Order Rate Constants ($k_{Pyr} \times 10^0/M^{-1}\ s^{-1}$) of the Reactions of 1,2-Phenylene Phosphorochloridate (**1*c***) with XC_5H_4N in MeCN at –25.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
k_{Pyr} $\times 10^0$	7.97 ± 0.05	5.26 ± 0.02	3.28 ± 0.03	2.25 ± 0.02	1.82 ± 0.01	1.71 ± 0.02	1.36 ± 0.01	1.32 ± 0.01	1.17 ± 0.01	1.11 ± 0.01	1.02 ± 0.01

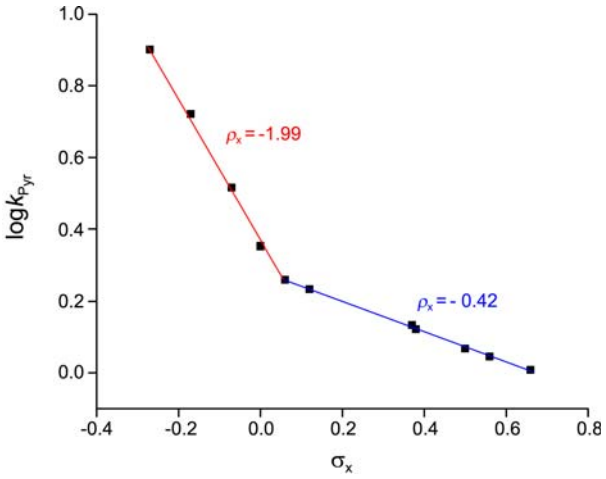


Figure 1. The Hammett plot (log k_{Pyr} *vs* σ_X) of the reactions of 1,2-phenylene phosphorochloridate (**1*c***) with X-pyridines in MeCN at –25.0 °C. The values of ρ_X are –1.99 ± 0.01 (r = 0.999) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph) and –0.42 ± 0.01 (r = 0.999) with X = (3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

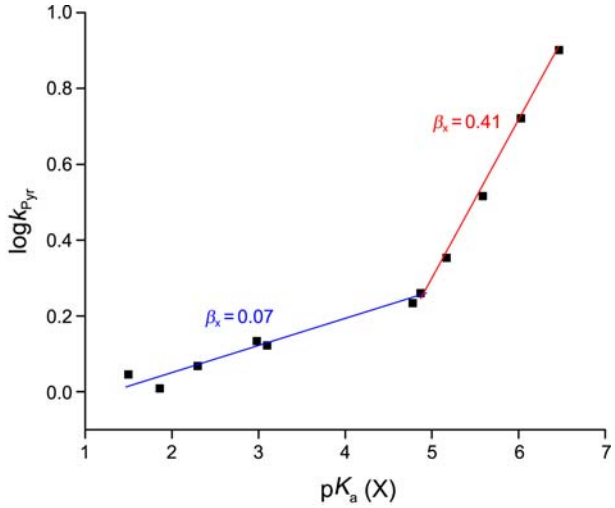


Figure 2. The Brönsted plot [log k_{Pyr} *vs* pK_a(X)] of the reactions of 1,2-phenylene phosphorochloridate (**1*c***) with X-pyridines in MeCN at –25.0 °C. The values of β_X are 0.41 ± 0.02 (r = 0.998) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph) and 0.07 ± 0.02 (r = 0.978) with X = (3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

The Brönsted β_X value was calculated by correlating log k_{Pyr}(MeCN) with p$K_a(H_2O)$,[3] which was justified theoretically and experimentally.[4] The rate increases with a more electron-donating substituent X in the nucleophile, consistent with a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom in the transition state (TS). However, both the Hammett (Fig. 1; log k_{Pyr} *vs* σ_X) and Brönsted [Fig. 2; log k_{Pyr} *vs* pK_a(X)] plots for substituent X variations in the nucleophiles are biphasic concave upwards with a break point at X = 3-Ph. The magnitudes of ρ_X (= –1.99) and β_X (= 0.41) values with the strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph) are much greater than those (ρ_X = –0.42 and β_X = 0.07) with the weakly basic pyridines (X = 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

The natural bond order (NBO) charges at the reaction center P atom in the substrate in the gas phase [B3LYP/6-311+G(d,p) level of theory],[5] second-order rate constants (k_{Pyr} and k_{An}) with unsubstituted pyridine (C_5H_5N) at 35.0 °C and aniline ($C_6H_5NH_2$) at 55.0 °C, Brönsted coefficients ($\beta_{X,Pyr}$ and $\beta_{X,An}$), and rate ratios of the pyridinolysis with C_5H_5N at 35.0 °C to the anilinolysis with $C_6H_5NH_2$ at 55.0 °C [k_{Pyr}(35.0 °C)/k_{An}(55.0 °C)] for the pyridinolyses and anilinolyses of **1*c***, **1*a***, **2*c***, and **2*a*** in MeCN are summarized in Table 2. The magnitudes of the positive charge at the

Table 2. Summary of the NBO Charges at the Reaction Center P Atom, Second-Order Rate Constants (k_{Pyr} with C_5H_5N at 35.0 °C and k_{An} with $C_6H_5NH_2$ at 55.0 °C), Brönsted coefficients ($\beta_{X,Pyr}$ and $\beta_{X,An}$), and Rate Ratios of the Pyridinolysis to Anilinolysis [k_{Pyr}(35.0 °C)/k_{An}(55.0 °C)] for the Pyridinolyses (XC_5H_4N) and Anilinolyses ($XC_6H_4NH_2$) of **1*c***, **1*a***, **2*c***, and **2*a*** in MeCN

Substrate	Charge at P	$k_{Pyr} \times 10^3$[a]	$\beta_{X,Pry}$	$k_{An} \times 10^3$[f]	$\beta_{X,An}$	k_{Pyr}/k_{An}[j]
1*c*: $C_6H_4O_2P(=O)Cl$	2.174	9,560,000[b]	0.41/0.07[e]	306,000[g]	1.54/0.35[i]	31
1*a*: (EtO)(PhO)P(=O)Cl	2.233	35.4[c]	0.99[c]	2.00	1.13	18
2*c*: $cC_2H_4O_2P(=O)Cl$	2.196	3,180,000[d]	1.06/–0.41[e]	11,800[h]	1.56/0.79[i]	270
2*a*: $(EtO)_2P(=O)Cl$	2.236	52.8	0.73	2.82	1.06	19

[a]The second-order rate constant with unsubstituted pyridine in MeCN at 35.0 °C. [b]Extrapolated value in the Arrhenius plot with kinetic data: k_{Pyr} = 2,250 (± 20), 4,980 (± 30), and 11,800 (± 100) × 10^{-3} M^{-1} s^{-1} at –25.0, –20.0, and –15.0 °C, respectively. [c]Unpublished data. [d]Extrapolated value in the Arrhenius plot with kinetic data: k_{Pyr} = 99.8, 289, and 885 × 10^{-3} M^{-1} s^{-1} at –20.0, –15.0, and –10.0 °C, respectively. See ref. 1s. [e]Strongly basic/weakly basic pyridines. [f]The second-order rate constant with unsubstituted aniline in MeCN at 55.0 °C. [g]Extrapolated value in the Arrhenius plot with kinetic data: k_{An} = 531, 863, 1,530, and 2,460 × 10^{-3} M^{-1} s^{-1} at –20.0, –15.0, –10.0, and –5.0 °C, respectively. See ref. 2s. [h]Extrapolated value in the Arrhenius plot with kinetic data: k_{An} = 0.671, 4.56, 11.1, and 26.6 × 10^{-3} M^{-1} s^{-1} at –5.0, 5.0, 10.0, and 15.0 °C, respectively. See ref. 2u. [i]Strongly basic/weakly basic anilines. [j]The rate ratio of the pyridinolysis with C_5H_5N at 35.0 °C to the anilinolysis with $C_6H_5NH_2$ at 55.0 °C.

reaction center P atom of cyclic five-membered rings are smaller than those of their acyclic counterparts. However, both the pyridinolysis and anilinolysis rates of cyclic five-membered rings are much faster than those of their acyclic counterparts, implying that the magnitude of the positive charge of the reaction center P atom (i.e., electrophilicity of the substrate) does not play any role to determine the rate.

The pyridinolysis rates are considerably faster than the anilinolysis rates of **1*c***, **1*a***, **2*c***, and **2*a***. Note that the second-order rate constants of the pyridinolysis are obtained at 35.0 °C while those of the anilinolysis are obtained at 55.0 °C. Considering the reaction temperature difference of 20.0 °C between the pyridinolysis and anilinolysis, the rate ratio of k_{Pyr}/k_{An} at the same temperature must be greater than k_{Pyr} (35.0 °C)/k_{An}(55.0 °C) in Table 2. The pK_a values of pyridine and aniline are 12.33 and 10.56 in MeCN[6] (and 5.17 and 4.58 in water),[7] respectively. Even taking into account the greater basicity of pyridine than that of aniline, $\Delta pK_a = 1.77$ in MeCN (and $\Delta pK_a = 0.59$ in water), the pyridinolysis rate is still much faster than the anilinolysis rate.[8] The difference in the rate may be due to resonance energy gain from the benzyl cation type π-complex formation[9] of pyridine with an empty d-orbital of the P atom. This type of π-complex is not possible with aniline because the lone pair on the amino nitrogen is a p-type so that the horizontal π-cloud of the ring overlap with the d-orbital of P marginally. Moreover, regarding the steric effects of the two ligands, the horizontal approach of the aniline ring should cause excessive steric hindrance in contrast to a much less steric effects in the vertical approach of the pyridine ring.[1a,m]

Both the pyridinolysis and anilinolysis rates of cyclic five-membered rings are much faster (10^3-10^5) than their acyclic counterparts: k_{Pyr}(**1*c***)/k_{Pyr}(**1*a***) = 2.70 × 10^5; k_{Pyr}(**2*c***)/k_{Pyr}(**2*a***) = 6.02 × 10^4; k_{An}(**1*c***)/k_{An}(**1*a***) = 1.53 × 10^5; k_{An}(**2*c***)/k_{An}(**2*a***) = 4.18 × 10^3. Both the pyridinolysis and anilinolysis rates of **1*c*** are faster than **2*c***: k_{Pyr}(**1*c***)/k_{Pyr}(**2*c***) = 3.01 and k_{An}(**1*c***)/k_{An}(**2*c***) = 25.9. In the case of acyclic counterparts, on the contrary, both the pyridinolysis and anilinolysis rates of **1*a*** are slower than **2*a***: k_{Pyr}(**1*a***)/k_{Pyr}(**2*a***) = 0.67 and k_{An}(**1*a***)/k_{An}(**2*a***) = 0.71. All these results suggest that the major factor to determine the aminolysis rates of cyclic substrates is different from that of their acyclic counterparts.

The activation parameters for the pyridinolyses with C_5H_5N and anilinolyses with $C_6H_5NH_2$ of **1*c***, **1*a***, **2*c***, and **2*a*** in MeCN are summarized in Table 3. The distinction of the activation parameters between cyclic substrates and their acyclic counterparts is much greater enthalpies and entropies of activation with cyclic substrates compared to those with their acyclic counterparts. The enthalpies of activation of cyclic substrates are greater ($\Delta\Delta H^{\neq}$ = 7-22 kcal/mol) than their acyclic counterparts, indicating that the aminolyses of acyclic substrates is more favorable than those of their cyclic counterparts. On the contrary, the entropies of activation of cyclic substrates are greater ($\Delta\Delta S^{\neq}$ = 44-93 eu; equivalent to $T\Delta\Delta S^{\neq}$ = 13-28 kcal/mol) than their acyclic counterparts, indicating that the aminolyses of cyclic substrates is much more favorable than those of their acyclic counterparts, due to unusual very large *positive* (or very small negative) values of the entropy of activation of cyclic substrates. In other words, the much faster aminolysis rates of cyclic substrates compared to their acyclic counterparts are ascribed to favorable entropy of activation change ($\Delta\Delta S^{\neq} >> 0$) over unfavorable enthalpy of activation change ($\Delta\Delta H^{\neq} >> 0$).[10]

Focus now shifts to the interpretation of large enthalpies of activation and large positive (or small negative) entropies of activation for the aminolyses of the studied cyclic substrates. The authors reported that the exceptionally much faster aminolysis rates of cyclic substrates than their acyclic counterparts are not due to a ring strain release or stereo-electronic effect,[1s,2s,u] supported by comparing with base catalyzed hydrolyses of cyclic five-membered rings (2-oxo-2-phenyl-1,2-oxaphospholane and 2-oxo-2-phenyl-1,3,2-dioxaphospholane) and their acyclic counterparts [ethyl ethyl(phenyl)phosphinate and diethyl phenylphosphonate].[11] These results suggest that the much faster aminolysis rates of the studied cyclic substrates than their acyclic counterparts are ascribed to the unusual solvent effects.

Winstein and Fainberg studied the S_N1 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 $\Delta S^{\neq}$ (= +12 eu) value for the reaction in water, while negative $\Delta S^{\neq}$ (= –2 to –4 eu; relatively constant *ca.* –3 eu) values in the first five sovents.[12] As the solvent is changed from ethanol to water, the rate of solvolysis dramatically increases by a factor of 3.35 × 10^5. Moreover, the rate ratio of k(formamide)/k(water) = 1.29 × 10^{-3} is not substantiated by the normal solvent effect,[13] completely contrary to expectation for the Hughes-Ingold rule,[14] since the solvent polarity of formamide (dielectric constant ε_r = 109.5) is greater than that of water (ε_r = 78.4). The unusual fast solvolysis rate in water was rationalized by the highly ordered water structure breaking, resulting in the large

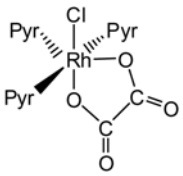
Table 3. Activation Parameters[a] for the Pyridinolyses with C_5H_5N and Anilinolyses with $C_6H_5NH_2$ of **1*c***, **1*a***, **2*c***, and **2*a*** in MeCN

Substrate	$\Delta H_{Pyr}^{\neq}$	$\Delta S_{Pyr}^{\neq}$	$-T\Delta S_{Pyr}^{\neq}$	$\Delta G_{Pyr}^{\neq}$	$\Delta H_{An}^{\neq}$	$\Delta S_{An}^{\neq}$	$-T\Delta S_{An}^{\neq}$	$\Delta G_{An}^{\neq}$
1*c*: $C_6H_4O_2P(=O)Cl$	20.5	+26	–8.0	12.5	13.3	–7	2.2	15.5
1*a*: (EtO)(PhO)P(=O)Cl	12.7	–24	7.4	20.1	6.8	–51	16.5	23.3
2*c*: $cC_2H_4O_2P(=O)Cl$	28.4	+49	–15.2	13.2	27.7	+30	–10.0	17.7
2*a*: $(EtO)_2P(=O)Cl$	6.3	–44	13.6	19.9	8.3	–45	14.8	23.1

[a]The values of activation parameters of the pyridinolyses are at 35.0 °C, while those of the anilinolyses are at 55.0 °C. See 'supplementary materials' in which the calculations of activation parameters ($\Delta H_{Pyr}^{\neq}$, $\Delta S_{Pyr}^{\neq}$, and $\Delta G_{Pyr}^{\neq}$ at 35.0 °C) of the present work (**1*c***) are described. The units of $\Delta H^{\neq}$, $-T\Delta S^{\neq}$, and $\Delta G^{\neq}$ are kcal/mol and the unit of $\Delta S^{\neq}$ is eu (cal mol^{-1} K^{-1}).

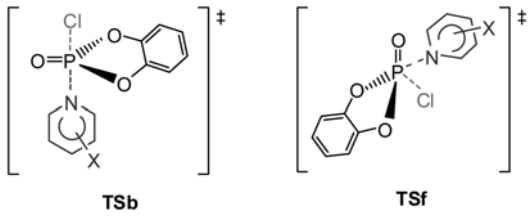
positive $\Delta S^{\neq}$ (= +12 eu) value and huge entropy of activation effect on the rate.[12] The authors reported that the five-membered rings of **1*c*** and **2*c*** are not in an apical-equatorial position but an equatorial position in the TS.[1s] Accordingly, the steric congestion between cyclic five-membered ring and pyridine nucleophile becomes much greater in the TS, resulting in greater value of the enthalpy of activation. The aminolysis is the bimolecular reaction, in which the two molecules of reactants in the GS becomes one activated complex in the TS. In general, the negative value of entropy of activation is obtained for the bimolecular nucleophilic substitution reaction as seen in the aminolyses of **1*a*** and 2***a***. Thus, great positive (or very small negative) values of the entropies of activation of the aminolyses [$\Delta S_{Pyr}^{\neq}$ = +26(**1*c***), +49(**2*c***), and $\Delta S_{An}^{\neq}$ = –7(**1*c***), +30(**2*c***) eu] suggest that the enormous degree of 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.

This suggestion may be partially supported by the following study. The chloro-oxalato-tripyridine-rhodium (III) complex (**I**) dissolves in a 1:1 mixture of pyridine and water, but not in either pure water or pyridine.[15] Presumably, a Gibbs free energy of solvation large enough to overcome the lattice force is obtained only by selective solvation of the three pyridine ligands by pyridine, and of the oxalato ligands by water,[15] indicating that the degree of solvation of complex (**I**)-type by dipolar aprotic solvent is too small to dissolve the complex. The composition of octahedral complex (**I**) is more or less similar to that of TS of the pyridinolysis of **2*c*** (and **1*c***) containing a cyclic five-membered ring with the two oxygen atoms, one pyridine, and one chlorine. Thus, the authors postulate that the ordered acetonitrile structure breaking occurs from the GS to the TS for the aminolysis of cyclic five membered ring, and the degree of the ordered acetonitrile structure breaking for the anilinolysis is greater than that for the pyridinolysis on the basis of the greater value of entropy of activation for the pyridinolysis compare to that for the anilinolysis.



Chloro-oxalato-tripyridine-rhodium (III) complex (**I**)

Biphasic concave upward free energy correlations for substituent X variations in the nucleophiles were observed for the pyridinolyses of dimethyl phosphinic chloride,[1h] dicyclohexyl phosphinic chloride,[1n] diisopropyl chlorophosphate,[1q] ethylene phosphorochloridate (**2*c***),[1s] dimethyl thiophosphinic chloride,[1h] diethyl thiophosphinic chloride,[1p] diphenyl thiophosphinic chloride,[1d] dimethyl chlorothiophosphate,[1g] and diethyl chlorothiophosphate,[1g] in which the



Scheme 3. Backside attack TSb and frontside attack TSf.

greater values of selectivity parameters with the strongly basic pyridines were obtained compared to those with the weakly basic pyridines. A concerted S_N2 mechanism was proposed and biphasic concave upward free energy correlations was rationalized by a change of nucleophilic attacking direction from a frontside attack TSf with the strongly basic pyridines to a backside attack TSb with the weakly basic pyridines. In the present work, accordingly, the authors propose a concerted mechanism involving a change of nucleophilic attacking direction from a frontside attack TSf (ρ_X = –1.99 and β_X = 0.41) with the strongly basic pyridines to a backside attack TSb (ρ_X = –0.42 and β_X = 0.07) with the weakly basic pyridines (Scheme 3). It is worthy of note that a frontside attack TSf yields greater magnitudes of ρ_X and β_X values compared to a backside attack.[1c]

Experimental Section

Materials. 1,2-Phenylene phosphorochloridate, commercially available, was used for kinetic studies without further purification. The HPLC grade acetonitrile (less than 0.005% water content) was used without further purification.

Kinetic Measurements. Rates were measured conductometrically as previously described.[1,2] The initial concentrations of [substrate] = 5.0×10^{-4} M and [X-pyridine] = (0.05-0.30) M were used for the present work. Pseudo-first-order rate constant values were the average of at least three runs that were reproducible within ± 3%.

Product Analysis. 1,2-Phenylene phosphorochloridate was reacted with excess pyridine, for more than 15 half-lives in MeCN at –25.0 °C. Solvent was removed under reduced pressure. The product was isolated after treatment with ether and acetonitrile, and then dried under reduced pressure. The analytical and spectroscopic data of the product are summarized as follows (see supplementary materials):

$[(C_6H_4O_2)P(=O)NC_5H_5]^+Cl^-$. White solid crystal; mp 109.0-110.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$ & TMS) δ 6.87-8.64 (aromatic, 9H, m); ^{13}C NMR (100 MHz, $CDCl_3$ & TMS) δ 111.75-148.29 (aromatic, 11C, m); ^{31}P NMR (162 MHz, $CDCl_3$ & TMS) δ 1.61 (P=O, 1P, s); LC-MS for $C_{11}H_9ClNO_3P$ (EI, *m/z*), 269 (M^+).

Acknowledgments. This work was supported by Inha University Research Grant.

References and Notes

1. (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 12.

(b) Lee, H. W.; Guha, A. K.; Kim, C. K.; Lee, I. *J. Org. Chem.* **2002**, *67*, 2215. (c) Adhikary, K. K.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc*. **2003**, *24*, 1135. (d) Hoque, M. E. U.; Dey, N. K.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Bull. Korean Chem. Soc*. **2007**, *28*, 1797. (e) Adhikary, K. K.; Lumbiny, B. J.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc*. **2008**, *29*, 851. (f) Lumbiny, B. J.; Adhikary, K. K.; Lee, B. S.; Lee, H. W. *Bull. Korean Chem. Soc*. **2008**, *29*, 1769. (g) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, H. W. *J. Phys. Org. Chem.* **2010**, *23*, 1022. (h) Dey, N. K.; Adhikary, K. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc*. **2010**, *31*, 3856. (i) Dey, N. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 709. (j) Hoque, M. E. U.; Dey, S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 1138. (k) Guha, A. K.; Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 1375. (l) Guha, A. K.; Kim, C. K.; Lee, H. W. *J. Phys. Org. Chem.* **2011**, *24*, 474. (m) Adhikary, K. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1945. (n) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2109. (o) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2339. (p) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 2805. (q) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 3505. (r) Adhikary, K. K.; Lumbiny, B. J.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 3743. (s) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 4347. (v) Unpublished data.

2. (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1999**, 765. (b) Lee, H. W.; Guha, A. K.; Lee, I. *Int. J. Chem. Kinet*. **2002**, *34*, 632. (c) Hoque, M. E. U.; Dey, S.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Org. Chem.* **2007**, *72*, 5493. (d) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 936. (e) Dey, N. K.; Han, I. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 2003. (f) Hoque, M. E. U.; Dey, N. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2007**, *5*, 3944. (g) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2008**, *21*, 544. (h) Lumbiny, B. J.; Lee, H. W. *Bull. Korean Chem. Soc*. **2008**, *29*, 2065. (i) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2009**, *22*, 425. (j) Dey, N. K.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc*. **2009**, *30*, 975. (k) Hoque, M. E. U.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem*. **2009**, *7*, 2919. (l) Dey, N. K.; Lee, H. W. *Bull. Korean Chem. Soc*. **2010**, *31*, 1403. (m) Dey, N. K.; Kim, C. K.; Lee, H. W. *Org. Biomol. Chem*. **2011**, *9*, 717. (n) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1939. (o) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 1997. (p) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2306. (q) Adhikary, K. K.; Lumbiny, B. J.; Dey, S.; Lee, H. W. *Bull. Korean Chem. Soc*. **2011**, *32*, 2628. (r) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3245. (s) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3355. (t) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3783. (u) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 4185.
3. The pK_a(H_2O) values of X-pyridines were taken from: (a) Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591. (b) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; Chapter 8.
4. (a) Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302. (b) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 45.
5. Hehre, W. J.; Random, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; Chapter 4.
6. Coetzee, J. F.; Padmanabhan, G. R. *J. Am. Chem. Soc*. **1965**, *87*, 5006.
7. (a) Brown, H. C.; McDaniel, D. H.; Hafliger, O. *Determination of Organic Structures by Physical Methods*; Braude, E. A., Nachode, F. C., Eds.; Academic Press Inc.: New York, N. Y. 1955. (b) Streitwieser, A., Jr.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*, 4th ed.; Macmillan: New York, 1992; p 735.
8. See ref. 1a for detailed discussion. Herein, the pyridinolysis rate is compared with the anilinolysis rate of isobasic aniline.
9. Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, 1969; p 358.
10. See refs. 1s, 2s, and 2u for detailed discussion about huge contribution of entropy of activation to the aminolysis rates of cyclic substrates.
11. (a) Westheimer, F. H. *Acc. Chem. Res*. **1968**, *1*, 70. (b) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047. (c) Yang, J. C.; Gorenstein, D. G. *Tetrahedron* **1987**, *43*, 479.
12. (a) Winstein, S.; Fainberg, A. H. *J. Am. Chem. Soc*. **1956**, *78*, 2770. (b) Winstein, S.; Fainberg, A. H. *J. Am. Chem. Soc*. **1957**, *79*, 5937.
13. The solvent effect on the S_N1 solvolyses of 2-chloro-2-methylpropane in six solvents at 25 °C is one of the examples of limitations of the Hughes-Ingold rules.
14. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; 2nd ed. Cornell University Press: Ithaca/N.Y. and London, 1969; p 457.
15. Gillard, R. D.; McKenzie, E. D.; Ross, M. D. *J. Inorg. Nucl. Chem.* **1966**, *28*, 1429.