Kinetics and Mechanism of the Pyridinolysis of Bis(2,6-dimethylphenyl) Chlorophosphate 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 September 9, 2011, Accepted September 26, 2011

The nucleophilic substitution reactions of bis(2,6-dimethylphenyl) chlorophosphate (**5**), containing the four *ortho*-methyl substituents, with X-pyridines are investigated kinetically in MeCN at 65.0 °C. The free energy correlations for substituent X variations in the nucleophiles exhibit biphasic concave upwards with a breakpoint at a X = 3-Cl. Unusual positive ρ_X (= +5.40) and negative β_X (= –0.83) values are obtained with the weakly basic pyridines. The pyridinolysis rate of **5** is hundreds times slower compared to that of bis(phenyl) chlorophosphate because of the steric hindrance of the four *ortho*-methyl substituents in the two phenyl rings. Ion-pair mechanism is proposed and positive ρ_X and negative β_X values are substantiated by an imbalance of the transition state.

Key Words : Phosphoryl transfer reaction, Pyridinolysis, Bis(2,6-dimethylphenyl) chlorophosphate, Biphasic concave upward free energy correlation, Transition state imbalance

Introduction

Kinetic studies of phosphoryl and thiophosphoryl transfer reactions have been studied experimentally (pyridinolysis,[1] anilinolysis,[2] and benzylaminolysis[3]) and theoretically[4] by this lab. Various kinds of substrates with chloride, phenoxide, thiophenoxide, isothiocyanate, and anilinide leaving groups are studied experimentally as follows: chlorophosphates [$(R_1O)(R_2O)P(=O)Cl$]; chlorothiophosphates [$(R_1O)-(R_2O)P(=S)Cl$]; phosphorothioates [$(R_1O)(R_2O)P(=O)SC_6H_4Z$]; phosphates [$(R_1O)(R_2O)P(=O)LG$ where LG = OC_6H_4Z or NCS]; phosphonochloridothioates [$R_1(R_2O)P(=S)Cl$]; phosphinic chlorides [$R_1R_2P(=O)Cl$]; thiophosphinic chlorides [$R_1R_2P(=S)Cl$]; phosphinates [$R_1R_2P(=O)OC_6H_4Z$]; and phosphinic amides [$R_1R_2P(=O)NHC_6H_4Z$], where R_1 and R_2 are alkyl and/or phenyl and/or aryl. The employed solvent is mainly acetonitrile (MeCN), and sometimes dimethyl sulfoxide (DMSO) is employed when the rate is too slow to obtain the rate constant in MeCN.

Herein, continuing the kinetic studies of the pyridinolyses of dimethyl [**1**: $(MeO)_2P(=O)Cl$],[1g] diethyl [**2**: $(EtO)_2P(=O)Cl$],[1g] diisopropyl [**3**: $(i\text{-}PrO)_2P(=O)Cl$],[1q] and Y-aryl phenyl [**4**: $(PhO)(YC_6H_4O)P(=O)Cl$][1a] chlorophosphates, the nucleophilic substitution reactions of bis(2,6-dimethylphenyl) chlorophosphate {**5**: $[2,6\text{-}(CH_3)_2\text{-}C_6H_3O]_2P(=O)Cl$} with X-

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

Scheme 1. The studied reaction system.

pyridines are investigated kinetically in MeCN at 65.0 ± 0.1 °C (Scheme 1) to gain further information into the reactivity and mechanism depending on the variation of the two ligands, R_1O and R_2O. Note that substrate **5** has four *ortho*-methyl substituents while substrate **4** has one *para*-Y substituent. The numbering of the substrates of **1-5** follows the sequence of the size of the two ligands, R_1O and R_2O: **5**$[2,6\text{-}(CH_3)_2\text{-}C_6H_3O]_2$ > **4**(PhO,YC_6H_4O) > **3**$(i\text{-}PrO)_2$ > **2**$(EtO)_2$ > **1**$(MeO)_2$.

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 of the reactions obeyed eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants were determined with at least five pyridine concentrations. The linear plots of eq. (1) suggest a lack of any base-catalysis or side reactions, and the overall reaction is described by Scheme 1.

$$k_{obsd} = k_0 + k_2 \,[XC_5H_4N] \tag{1}$$

The second-order rate constants [k_2 (M^{-1} s^{-1})] are summarized in Table 1. The Brönsted β_X value was calculated by correlating log k_2(MeCN) with pK_a(H_2O),[5] which was justified theoretically and experimentally.[6] The substituent effects of the nucleophiles upon the pyridinolysis rates do not correlate with those for a typical nucleophilic substitution reaction: (i) for more basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl), the stronger nucleophile leads to a faster rate with positive charge development at the nucleophilic N atom in the transition state (TS), resulting in negative ρ_X (= –4.78) and positive β_X (= +0.86) values; (ii) for less basic pyridines (X = 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN), on the contrary, the weaker nucleophile leads to

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/M^{-1} s^{-1}$) of the Reactions of Bis(2,6-dimethylphenyl) Chlorophosphate (**5**) with XC_5H_4N in MeCN at 65.0 ºC

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2 \times 10^4$	392 ± 2	125 ± 1	39.5 ± 0.3	18.3 ± 0.1	8.85 ± 0.03	4.94 ± 0.04	0.344 ± 0.001	0.515 ± 0.001	1.53 ± 0.01	3.89 ± 0.04	15.0 ± 0.1
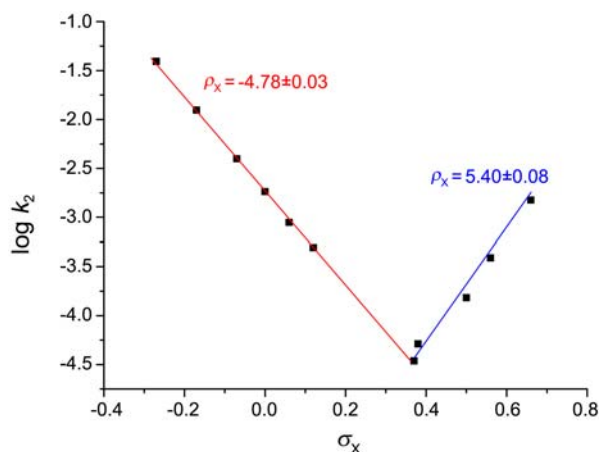
Figure 1. The Hammett plot (log k_2 *vs* σ_X) of the reactions of bis(2,6-dimethylphenyl) chlorophosphate (**5**) with X-pyridines in MeCN at 65.0 ºC. The values of ρ_X are –4.78 ± 0.03 (r = 0.999) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl) and 5.40 ± 0.08 (r = 0.991) with X = (3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).
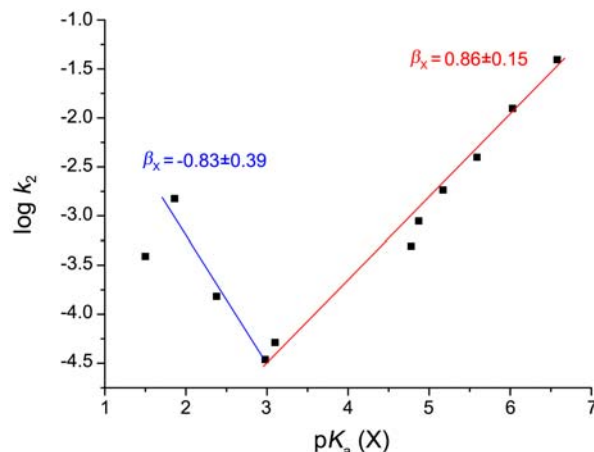
Figure 2. The Brönsted plot [log k_2 *vs* pK_a(X)] of the reactions of bis(2,6-dimethylphenyl) chlorophosphate (**5**) with X-pyridines in MeCN at 65.0 ºC. The values of β_X are 0.86 ± 0.15 (r = 0.991) and –0.83 ± 0.39 (r = 0.865) with X = (3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

a faster rate with negative charge development at the nucleophilic N atom in the TS, resulting in *unusual* great magnitudes of positive ρ_X (= +5.40) and negative β_X (= –0.83) values. Thus, the Hammett (Fig. 1; log k_2 *vs* σ_X) and Brönsted [Fig. 2; log k_2 *vs* pK_a(X)] plots are biphasic concave upwards with a break point at X = 3-Cl, giving min rate constant.

The second-order rate constants (k_2) with unsubstituted pyridine (C_5H_5N) at 35.0 ºC, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],[7] Brönsted coefficients (β_X), and cross-interaction constant (CIC; ρ_{XY})[8] for the pyridinolyses of five (R_1O)(R_2O)P(=O)Cl-type chlorophosphates in MeCN are summarized in Table 2. When the magnitude of the positive charge of the reaction center P atom in the substrate plays an important role to determine

the pyridinolysis rate, the sequence of the pyridinolysis rate should be **3** > **2** > **4** > **1** > **5**. On the other hand, when the steric effects of the two ligands (R_1O and R_2O) play an important role, the sequence of the rate should be **1** > **2** > **3** > **4** > **5**.

However, the observed sequence of the pyridinolysis rates is **4** > **1** > **2** > **3** >> **5**, giving the relative rate ratio of 650(**4**) : 160(**1**) : 130(**2**) : 24(**3**) : 1(**5**). The pyridinolysis rate of **5** is exceptionally slow [note k_2(**4** with Y = H)/k_2(**5**) = 650] and the sequence of the pyridinolysis rates does not have consistency with the magnitude of the positive charge of the reaction center P or steric effects of the two ligands. This suggests that the pyridinolysis rates of chlorophosphates are not dependent upon one dominant factor, while the anilinolysis rates of chlorophosphates are predominantly dependent

Table 2. Summary of the Second-Order Rate Constants ($k_2 \times 10^3/M^{-1} s^{-1}$ with C_5H_5N at 35.0 ºC), NBO Charges at the Reaction Center P Atom, Brönsted coefficients (β_X), and Cross-Interaction Constant for the Pyridinolyses (XC_5H_4N) of **1-5** in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	β_X	ρ_{XY}	ref
1: $(MeO)_2P(=O)Cl$	64.7	2.226	0.63[e]	–	1g
2: $(EtO)_2P(=O)Cl$	52.8	2.236	0.73[e]	–	1g
3: $(i\text{-}PrO)_2P(=O)Cl$	9.60	2.269	1.05[f]/0.39[g]	–	1q
4: $(PhO)(YC_6H_4O)P(=O)Cl$	266[b]	2.230[d]	0.16-0.18[h]	–0.15[h]	1a
5: $[2,6\text{-}(CH_3)_2C_6H_3O]_2P(=O)Cl$	0.407[c]	2.214	0.86[i]/–0.83[j]	–	this work

[a]Second-order rate constant with unsubstituted pyridine (X = H) at 35.0 ºC. [b]Extrapolated value in the Arrhenius plot with kinetic data: k_2 = 37.1, 94.0, and 135 × 10^{-3} M^{-1} s^{-1} at 5.0, 15.0, and 25.0 ºC, respectively, from ref. 1a. [c]Extrapolated value in the Arrhenius plot with kinetic data: k_2 = 0.688, 1.17, and 1.83 × 10^{-3} M^{-1} s^{-1} at 45.0, 55.0, and 65.0 ºC, respectively. [d]The value with Y = H. [e]The value at 35.0 ºC. [f]The value at 35.0 ºC. X = (4-MeO, 4-Me, 3-Me, H, 3-Ph). [g]The value at 35.0 ºC. X = (3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). [h]The value at 25.0 ºC. [i]The value at 65.0 ºC. X = (4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl). [j]The value at 65.0 ºC. X = (3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

upon the steric effects over the inductive effects of the two ligands, R_1O and R_2O.[2f,g,n,r,s]

The inductive effects of the two 2,6-dimethyl substituents on the pyridinolysis rate of **5** in MeCN at 35.0 ºC can be calculated roughly as follows:[9] (i) assuming that the inductive effects of 4-Me and 2(and 6)-Me are the same; (ii) assuming that the inductive effects of substituents Y are additive, i.e., no cross-interaction between 2- and 6-Me; (iii) according to the Hammett eq. $\log [k_2(Y)/k_2(H)] = \rho_Y\sigma_Y = 0.69\sigma_Y$[10] for the pyridinolysis of **4** with X = 4-Me and σ(4-Me) = –0.17; then, (iv) $k_2(5) = 90.3 \times 10^{-3}$ M^{-1} s^{-1} is obtained from $\log [k_2(5)/k_2(4$ with Y = H$)] = 0.69(4 \times -0.17)$. The calculated value of $k_2(5) = 90.3 \times 10^{-3}$ from the inductive effects of four *ortho*-methyl substituents is much greater (220 times greater) than the observed value of $k_2(5) = 0.407 \times 10^{-3}$ M^{-1} s^{-1}, strongly suggesting that another factor plays an important role over the inductive effects of four *ortho*-methyl substituents on the pyridinolysis rate of **5**.

Meanwhile, the pyridinolysis rate is rather faster than the corresponding anilinolysis rate in MeCN:[11] k_{Pyr}(35.0 ºC)/k_{An}(55.0 ºC) = 15(**1**),[1g,2g] 19(**2**),[1g,2g] 14(**3**),[1q,2r] and 300(**4**).[1a,2a] Note that the reaction temperatures are 35.0 and 55.0 ºC for the pyridinolysis and anilinolysis, respectively. The faster pyridinolysis rate may be due to resonance energy gain from the benzyl cation type π-complex formation 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 much less steric effects in the vertical approach of the pyridine ring.[1a]

The B3LYP/6-311+G(d,p) geometry, bond angles, and natural bond order (NBO) charges of **4** with Y = H and **5** in the gas phase are shown in Figure 3. The magnitude of positive charge at the reaction center P atom of **5** (+2.214) is smaller than that of **4** (+2.230) and the magnitude of negative charge at leaving group Cl atom of **5** (–2.277) is greater than that of **4** (–0.245) due to four *ortho*-methyl substituents in **5**. The different conformation of two phenyl rings between **4** and **5** in Figure 3 is meaningless,[12] since the rotation barrier of phenyl ring is so small that free rotations of phenyl or phenoxy group are very fast even taking into account the two 2,6-dimethyl substituents in **5**.[2f,13] The bond angle of R_1O and R_2O in **5** (98.9º) is smaller than that in **4** (100.7º). Nevertheless, it is evident that the two 2,6-dimethyl substituents in **5** sterically interrupt the attack of nucleophile towards the leaving group Cl, resulting in much slower aminolysis (pyridinolysis and anilinolysis[2t]) rate of **5** compared to that of **4**.

This suggestion is supported by the solvolytic behavior of 2,6-dimethylbenzoyl chloride, which was found to undergo solvolysis by an ionization mechanism because of the steric hindrance on the attack on acyl carbon from the presence of the two *ortho*-methyl groups, coupled with their electron supplying influence (*vide infra*).[13] Kevill and coworkers discussed "peculiar effects" of disubstituted *ortho*-groups mainly due to the steric phenomena by studying the solvolyses of 2,6-dichloro and 2,6-difluoro benzoyl chlorides in various solvents.[14] The authors also reported that the anilinolysis rate of **5** is much slower than **4** and the reaction mechanism is changed from a concerted process for **4** to stepwise process with a rate-limiting leaving group departure from the intermediate for **5** due to the severe steric hindrance of four *ortho*-methyl substituents in **5**.[2t]

A concerted mechanism with an early TS involving backside nucleophilic attack TSb towards the Cl leaving group (Scheme 2) was proposed on the basis of small negative CIC ($\rho_{XY} = -0.15$)[15] and small values of Brönsted coefficients ($\beta_X = 0.16$-0.18) for the pyridinolysis of **4**.[1a] The S$_N$2 reaction mechanism was proposed for the pyridinolyses of **1** and **2** with both frontside TSf and backside attacks TSb (Scheme 2), and the fraction of a frontside attack is more or less larger than that of a backside attack, on the basis of the magnitudes of β_X values.[1g] A concerted S$_N$2 mechanism was proposed and biphasic concave upward free energy correlations was rationalized by a change of nucleophilic attacking direction from a frontside attack TSf ($\beta_X = 1.05$) with the strongly
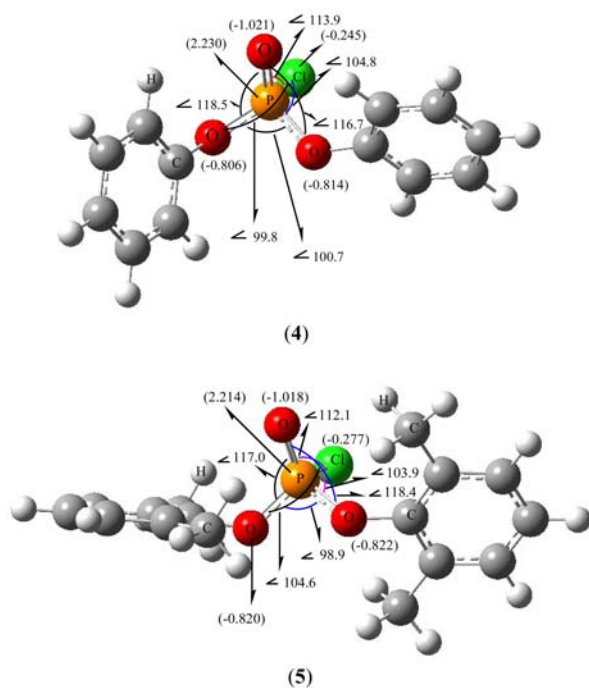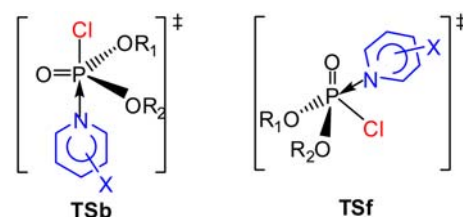

Figure 3. The B3LYP/6-311+G(d,p) geometry of bis(phenyl) chlorophosphate (**4** with Y = H) and bis(2,6-dimethylphenyl) chlorophosphate (**5**) in the gas phase.


Scheme 2. Backside and frontside attack TS.

basic pyridines to a backside attack (TSb; $\beta_X = 0.39$) with the weakly basic pyridines for the pyridinolysis of **3**.[1q] 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]

The free energy correlations for substituent X variations in the pyridines are linear for the pyridinolyses of **1**, **2**, and **4**. The biphasic concave upward Hammett and Brönsted plots with X were observed for the pyridinolyses of following substrates: **3**,[1q] dimethyl phosphinic chloride [Me$_2$P(=O)Cl];[1h] dicyclohexyl phosphinic chloride [(cHex)$_2$P(=O)Cl];[1n] dimethyl thiophosphinic chloride [Me$_2$P(=S)Cl];[1h] diethyl thiophosphinic chloride [Et$_2$P(=S)Cl];[1p] dimethyl chlorothiophosphate [(MeO)$_2$P(=S)Cl];[1g] diethyl chlorothiophosphate [(EtO)$_2$P(=S)Cl];[1g] diphenyl thiophosphinic chloride [Ph$_2$P(=S)Cl];[1d] Y-aryl phenyl chlorothiophosphates [(PhO)-(YC$_6$H$_4$O)P(=O)Cl];[1j] Y-aryl phenyl isothiocyanophosphates [(PhO)(YC$_6$H$_4$O)P(=O)NCS];[1c] and *O,O*-dimethyl *S*-aryl phosphorothioates [(MeO)$_2$P(=O)SC$_6$H$_4$Z].[1o] The biphasic concave upward free energy relationships were interpreted as a change of the nucleophilic attacking direction from a frontside attack TSf with the strongly basic pyridines to a backside attack TSb with the weakly basic pyridines in a concerted process. In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism, such as parallel reactions where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of the biphasic concave downward plot is diagnostic of a rate-limiting step change from bond breaking with less basic nucleophiles to bond formation with more basic nucleophiles.[16] It is the suggestion of the authors that the concave upward Hammett and Brönsted plots can also be diagnostic of a change in the attacking direction of the nucleophile depending on the substituents from backside to frontside.[1g]

The discrete linear free energy relationship was reported because of a desolvation step prior to the rate-limiting nucleophilic attack with a smaller value of β_X when the nucleophile is anion and the solvent is dipolar protic, e.g., water.[17] However, in the present work, the positive ρ_X (= +5.40) and negative β_X (= −0.83) values with the less basic pyridines are not ascribed to a desolvation step prior to the rate-limiting nucleophilic attack, since the substrate and nucleophile are neutral and the solvent of MeCN is not dipolar protic but aprotic. Thus, the authors rule out the desolvation of the ground state (GS) to rationalize the unusual positive ρ_X and negative β_X values with the weakly basic pyridines.

The authors reported that the sign of ρ_X changes from negative with the relatively strong electron-donating Y substituents (min; $\rho_X = -1.6$ with Y = 4-NO$_2$), *via* gradual increase of ρ_X values with Y, to positive with the more electron-withdrawing substituents (max; $\rho_X = +0.18$ with Y = 4-CH$_3$) of the reactions of 1-(Y-aryl)ethyl chlorides [YC$_6$H$_4$CH(CH$_3$)Cl] with X-anilines in methanol.[18] The anilinolyses of Y-benzhydryl chlorides [YC$_6$H$_4$CH(C$_6$H$_5$)Cl] in methanol also exhibited the change of the sign of ρ_X
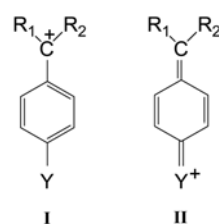
Scheme 3. Intermediate of cation. R$_1$ = H and R$_2$ = CH$_3$ or C$_6$H$_5$.

depending on Y substituents (min; $\rho_X = -0.76$ with Y = 4-NO$_2$ and max; $\rho_X = +0.95$ with Y = 4-CH$_3$).[19] The positive ρ_X values of both reaction systems were interpreted in terms of a TS structure in which nearly complete bond formation between the nucleophile and cation formed in an ion-pair pre-equilibrium is coupled with a TS imbalance phenomenon, advocated by Jencks and Bernasconi.[20] Two extreme forms of the cation intermediate are conceivable: no positive charge delocalization of **I** and completely positive charge delocalization of **II** (Scheme 3).[18,19]

When the aniline attacks and forms the N–C$_\alpha$ bond with the delocalized cation form of **II**, instantaneous charge delocalization and solvent reorganization cannot take place simultaneously, since delocalization of developing negative charge transferred from the N on aniline into the solvated positive charge at Y lags behind proton transfer, partly because C$_\alpha$ in this form has very low positive charge. As a result, negative charge accumulation on C$_\alpha$ in the TS, leading to positive ρ_X, prior to delocalization into Y$^+$ through the phenyl ring and reorganizes the solvent around Y$^+$ eventually.[18,19]

In the present work, the presence of the four *ortho*-methyl groups in the two phenyl rings, coupled with their electron supplying effect, leads the pyridinolysis to undergo by an ionization mechanism because of severe steric hindrance on the attack on phosphorus reaction center, as observed in the solvolysis of 2,6-dimethylbenzoyl chloride (*vide supra*).[13] Thus, it is the suggestion of the authors that the reaction proceeds through ion-pair mechanism involving fast pre-equilibrium between **5** and ion-pair (Scheme 4): (i) When the pyridine nucleophile is strong enough to overcome the steric hindrance of the four *ortho*-methyl substituents, direct substitution takes place on the phosphorus cation of the ion-pair, resulting in the negative ρ_X and positive β_X values
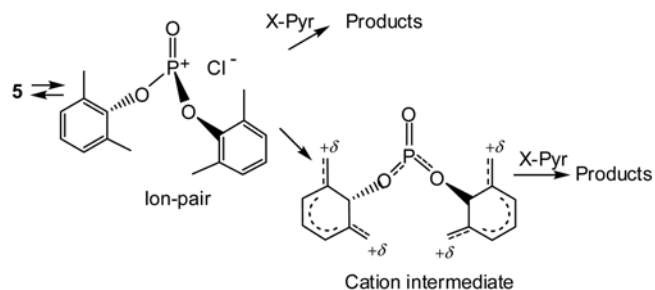
Scheme 4. Proposed mechanism of the reactions of **5** with X-pyridines: Upper route with the strongly basic pyridines and lower route with the weakly basic pyridines.

(upper route). (ii) When the pyridine nucleophile is so weak that pyridine cannot overcome the steric hindrance of the four *ortho*-methyl substituents, nucleophile attacks cation intermediate, resulting in the positive ρ_X and negative β_X values due to a TS imbalance phenomenon[20] (lower route), as observed in the anilinolysis of 1-(Y-aryl)ethyl chlorides[18] and Y-benzhydryl chlorides.[19]

Experimental Section

Materials. Bis(2,6-dimethylphenyl)chlorophosphate was used for kinetic studies without further purification. The HPLC grade acetonitrile (less than 0.005% water content), diethyl ether and n-hexane were used without further purification.

Kinetic Measurement. Rates were measured conductometrically as previously described.[1,2] [Substrate] = 5.0×10^{-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 $\pm$ 3%.

Product Analysis. Bis(2,6-dimethylphenyl)chlorophosphate was reacted with excess 4-methylpyridine, for more than 15 half-lives at 65.0°C in MeCN. Solvent was removed under reduced pressure. The product was isolated after treatment with ether and acetonitrile, then dried under reduced pressure using oil diffusion pump. The analytical and spectroscopic data of the product are summarized as follows:

[(C$_{16}$H$_{18}$O$_2$)P(=O)NC$_5$H$_4$-4-CH$_3$]$^+$Cl$^-$. White crystal solid, mp (149-150) °C; ^{1}H NMR (400 MHz, CDCl$_3$ & TMS) δ 2.70 (aliphatic, 15H, s), 7.74-8.68 (aromatic, 10H, m); ^{13}C NMR (100 MHz, CDCl$_3$ & TMS) δ 15.27-17.05 (aliphatic, 5C, m), 124.51-149.05 (aromatic, 17C, m); ^{31}P NMR (162 MHz, CDCl$_3$ & TMS) δ −13.85 (P=O, 1P, s); C$_{22}$H$_{25}$NO$_3$P$^+$ *m/z*, 382 (M$^+$).

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10. The value of ρ_Y for the pyridinolysis of **4** with X = 4-Me is at 25.0 °C.
11. The anilinolysis rate of **5** was too slow to gain the rate constant even at 75.0 °C in MeCN (note that the boiling point of MeCN is 81.6 °C). Thus, the anilinolysis of **5** was carried out in DMSO at 55.0 °C.
12. The calculated (RHF/6-31G* level of theory) phenyl group rotation barrier of **4** (with Y = H) in the gas phase is 1.6 kcal/mol when the remaining part except one phenyl group is fixed, but 2.9 kcal/mol when the conformations are changed with the phenyl group rotations. The calculated phenoxy group rotation barriers of **4** (with Y = H) is 18.8 kcal/mol when the remaining part, except one phenoxy group, is fixed. These results may show that the free rotations of phenyl or phenoxy group are also very fast. Detailed data is available in ref. 2f. House and his coworkers reported the

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