

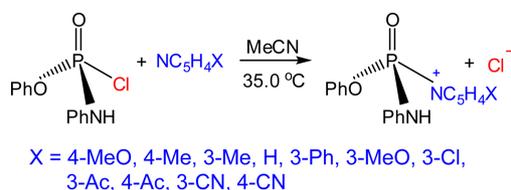
Pyridinolysis of Phenyl *N*-Phenyl Phosphoramidochloridate in Acetonitrile

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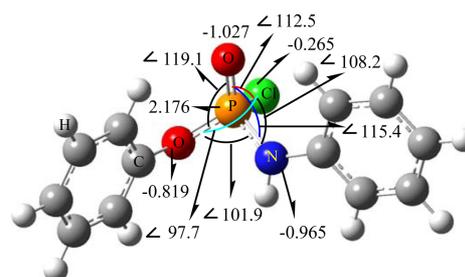
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Received February 20, 2012, Accepted June 30, 2012**Key Words** : Phosphoryl transfer reaction, Pyridinolysis, Phenyl *N*-phenyl phosphoramidochloridate

Kinetics and mechanism of the aminolyses for various substrates have been studied extensively by this lab. The studied substrates are dominantly (R<sub>1</sub>O)(R<sub>2</sub>O)P(=O) or S)Cl and R<sub>1</sub>R<sub>2</sub>P(=O) or S)Cl-type where R<sub>1</sub> and R<sub>2</sub> are alkyl and/or phenyl (aryl). Herein, the nucleophilic substitution reactions of phenyl *N*-phenyl phosphoramidochloridate (**7**), involving anilino (C<sub>6</sub>H<sub>5</sub>NH) ligand, with X-pyridines are investigated kinetically in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1). The aim of this work is to gain further information into the reactivity and mechanism depending on the variation of the two ligands as well as to compare with the pyridinolyses of chlorophosphates: dimethyl [**1**: (MeO)<sub>2</sub>P(=O)Cl],<sup>1a</sup> diethyl [**2**: (EtO)<sub>2</sub>P(=O)Cl],<sup>1a</sup> dipropyl [**3**: (PrO)<sub>2</sub>P(=O)Cl],<sup>1b</sup> dibutyl [**4**: (BuO)<sub>2</sub>P(=O)Cl],<sup>1c</sup> diisopropyl [**5**: (*i*-PrO)<sub>2</sub>P(=O)Cl],<sup>1d</sup> and Y-aryl phenyl [**6**: (PhO)(YC<sub>6</sub>H<sub>4</sub>O)P(=O)Cl]<sup>1e</sup> chlorophosphates. The numbering of the substrates of **1-6** follows the sequence of the summation of the Taft steric constants of the two ligands, R<sub>1</sub> and R<sub>2</sub>: **6**[Y = H; (PhO)<sub>2</sub>] > **5**(*i*-PrO)<sub>2</sub> > **4**(BuO)<sub>2</sub> > **3**(PrO)<sub>2</sub> > **2**(EtO)<sub>2</sub> > **1**(MeO)<sub>2</sub> where E<sub>S</sub>(R) = -2.48(Ph); -0.47(*i*-Pr); -0.39(Bu); -0.36(Pr); -0.07(Et); 0.00(Me).<sup>2</sup> Note that the magnitude of E<sub>S</sub>(*i*-Pr) is larger than that of E<sub>S</sub>(Bu) although the size of *i*-Pr is smaller than that of Bu. The magnitude of E<sub>S</sub>(PhNH) in **7** must be larger than that of E<sub>S</sub>(PhO) in **6**.

The B3LYP/6-311+G(d,p) geometries, bond angles, and natural bond order (NBO) charges of **7** in the gas phase are shown in Figure 1.<sup>3</sup> The MO theoretical structure shows that the two oxygens, nitrogen, and chlorine have more or less distorted tetrahedral geometry with the phosphorus atom at the center. The degree of distortion of **7** (Δδ<sub>GS</sub> = 0.36) is



**Scheme 1.** The pyridinolysis of phenyl *N*-phenyl phosphoramidochloridate (**7**) in MeCN at 35.0 °C.



**Figure 1.** The B3LYP/6-311+G(d,p) geometries of phenyl *N*-phenyl phosphoramidochloridate (**7**) in the gas phase.

smaller than **6** (Δδ<sub>GS</sub> = 0.40).<sup>4</sup>

## 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 ( $k_{\text{obsd}}$ ) for all the reactions obeyed Eq. (1) with negligible  $k_0$  ( $\approx 0$ ) in MeCN. The clean 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 reaction, and the overall reaction is described by Scheme 1.

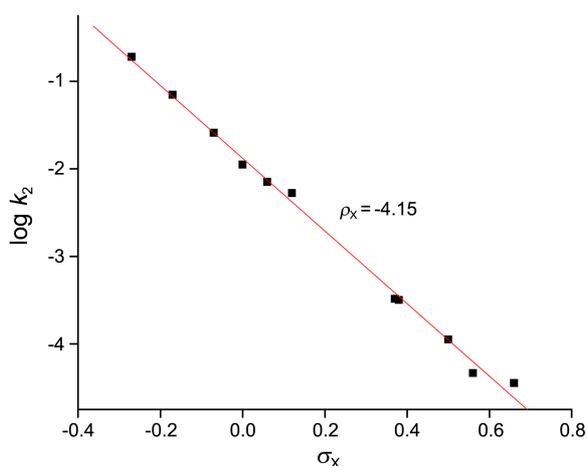
$$k_{\text{obsd}} = k_0 + k_2 [\text{XC}_5\text{H}_4\text{N}] \quad (1)$$

The second-order rate constants [ $k_2$  (M<sup>-1</sup> s<sup>-1</sup>)] are summarized in Table 1. The Brønsted β<sub>X</sub> value was calculated by correlating log  $k_2$ (MeCN) with pK<sub>a</sub>(H<sub>2</sub>O),<sup>5</sup> which was justified theoretically and experimentally.<sup>6</sup> The substituent effects (X) of the nucleophiles upon the pyridinolysis rates are compatible with those for a typical nucleophilic substitution reaction and 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<sub>X</sub> (= -4.15; Fig. 2) and positive β<sub>X</sub> (= 0.75; Fig. 3) values.

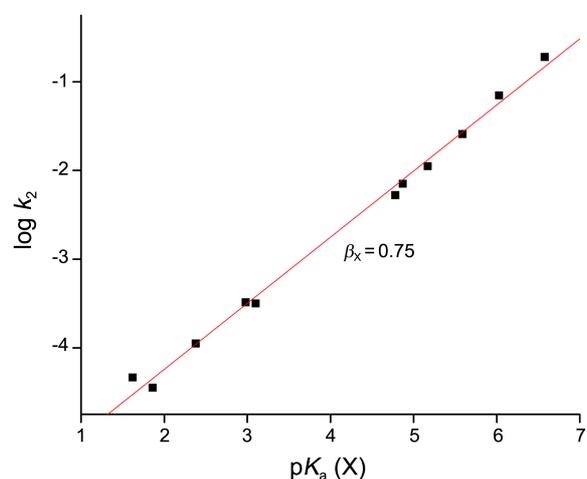
The second-order rate constants ( $k_2$ ) with unsubstituted

**Table 1.** Second-Order Rate Constants ( $k_2 \times 10^3/\text{M}^{-1} \text{s}^{-1}$ ) of the Reactions of Phenyl *N*-Phenyl Phosphoramidochloridate (**7**) with XC<sub>5</sub>H<sub>4</sub>N in MeCN at 35.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2$	191	70.3	25.7	11.2	7.07	5.27	0.327	0.317	0.112	0.0463	0.0355 ±
× 10 <sup>3</sup>	± 1	± 0.1	± 0.1	± 0.1	± 0.01	± 0.01	± 0.001	± 0.001	± 0.002	± 0.0001	0.0001



**Figure 2.** The Hammett plot ( $\log k_2$  vs  $\sigma_X$ ) of the reaction of phenyl *N*-phenyl phosphoramidochloridate (**7**) with X-pyridines in MeCN at 35.0 °C. The value of  $\rho_X$  is  $-4.15 \pm 0.09$  ( $r = 0.998$ ).



**Figure 3.** The Brønsted plot [ $\log k_2$  vs  $pK_a(X)$ ] of the reactions of phenyl *N*-phenyl phosphoramidochloridate (**7**) with X-pyridines in MeCN at 35.0 °C. The value of  $\beta_X$  is  $0.75 \pm 0.10$  ( $r = 0.997$ ).

pyridine ( $C_5H_5N$ ) at 35.0 °C, NBO charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],<sup>3</sup> summations of the Taft steric constants of  $R_1$  and

$R_2$  [ $\Sigma E_S = E_S(R_1) + E_S(R_2)$ ],<sup>2</sup> Brønsted coefficients ( $\beta_X$ ), cross-interaction constant (CIC;  $\rho_{XY}$ ),<sup>7</sup> and variation trends of the free energy relationships with X for the pyridinolyses of six  $(R_1O)(R_2O)P(=O)Cl$ -type chlorophosphates (**1-6**) and phenyl *N*-phenyl phosphoramidochloridate (**7**) in MeCN are summarized in Table 2. The NBO charge at the reaction center P atom with **5** (= 2.269) is the largest one, however, the pyridinolysis rate with **5** is the slowest one. These indicate that there is no correlation between the pyridinolysis rate and the magnitude of the positive charge of the reaction center P atom in the substrate, and that the inductive effects of the two ligands do not play any role to determine the pyridinolysis rate.

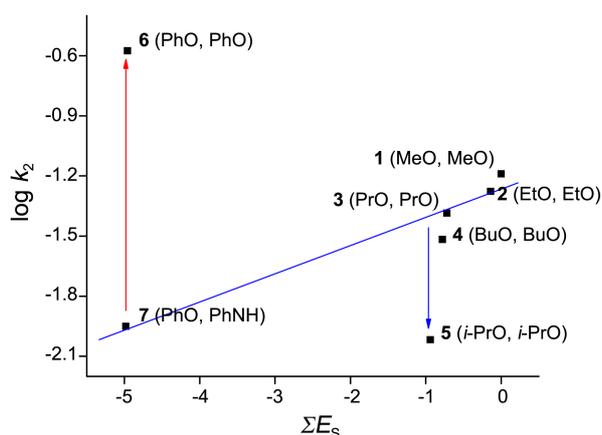
The pyridinolysis rates of **1-5** are inversely proportional to the summation of the steric constants of the two ligands ( $\Sigma E_S$ ), *i.e.*, the greater the steric hindrance of the two ligands, the rate becomes slower: **1** > **2** > **3** > **4** >> **5**. The sensitivity coefficients of  $\delta = 0.33$  ( $r = 0.938$ : qualitative correlation) and 0.64 ( $r = 0.816$ : rough correlation) are obtained for the pyridinolyses of **1-4** and **1-5**, respectively, according to the Taft eq. ( $\log k_2 = \delta \Sigma E_S + C$ ).<sup>2</sup> The pyridinolysis rate of **5** with two *i*-propyl ligands exhibits considerably negative deviation from the slope. The anilinolysis rate of **5** also exhibited great negative deviation from the slope, and the exceptionally slow rate cannot be rationalized by the normal stereoelectronic effect.<sup>8</sup> The pyridinolysis rate of **6** with two phenoxy ligands is exceptionally fast, as the anilinolysis rate of **6** also showed large positive deviation from the slope.<sup>9</sup> The pyridinolysis rate of **7** seems to follow the Taft eq. where the rate is predominantly dependent upon the steric effects over the inductive effects of the two ligands. The sensitivity coefficient of  $\delta = 0.14$  ( $r = 0.963$ : semi-quantitative correlation) is obtained for the pyridinolyses of five substrates of **1-4** and **7** (Fig. 4).<sup>10</sup> It should be noted that the value of  $\Sigma E_S$  is not ' $E_S(R_1O) + E_S(R_2O)$ ' but ' $E_S(R_1) + E_S(R_2)$ ' because of the lack of data of Taft steric constant of  $R_1O$ .

The  $\beta_X$  values may be divided into three groups: (i) relatively large values of 0.63–0.87 for five substrates of **1-4** and **7**; (ii) considerably large value of 1.05 with the strongly basic pyridines while relatively small value of 0.39 with the

**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 °C, NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants of  $R_1$  and  $R_2$  [ $\Sigma E_S = E_S(R_1) + E_S(R_2)$ ], Brønsted coefficients ( $\beta_X$ ), CIC ( $\rho_{XY}$ ), and Variation Trends of Free Energy Relationship with X for the Pyridinolyses ( $XC_5H_4N$ ) of **1-7** in MeCN

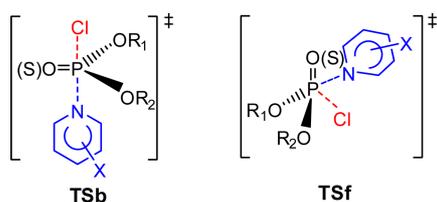
Substrate	$k_2 \times 10^3^a$	charge at P	$-\Sigma E_S^d$	$\beta_X$	$\rho_{XY}$	trend
<b>1:</b> (MeO) <sub>2</sub> P(=O)Cl	64.7	2.226	0.00	0.63	–	L <sup>f</sup>
<b>2:</b> (EtO) <sub>2</sub> P(=O)Cl	52.8	2.236	0.14	0.73	–	L
<b>3:</b> (PrO) <sub>2</sub> P(=O)Cl	41.2	2.239	0.72	0.87	–	L
<b>4:</b> (BuO) <sub>2</sub> P(=O)Cl	30.4	2.239	0.78	0.80	–	L
<b>5:</b> ( <i>i</i> -PrO) <sub>2</sub> P(=O)Cl	9.60	2.269	0.94	1.05/0.39 <sup>e</sup>	–	V <sup>g</sup>
<b>6:</b> (PhO)(YC <sub>6</sub> H <sub>4</sub> O)P(=O)Cl	266 <sup>b,c</sup>	2.230 <sup>b</sup>	4.96	0.16–0.18	–0.15	L
<b>7:</b> (PhO)(C <sub>6</sub> H <sub>5</sub> NH)P(=O)Cl	11.2	2.176	> 4.96	0.75	–	L

<sup>a</sup>Second-order rate constant with unsubstituted pyridine (X = H) in MeCN at 35.0 °C. <sup>b</sup>Y = H. <sup>c</sup>Extrapolated value. <sup>d</sup>Note that the value of  $\Sigma E_S$  is not ' $E_S(R_1O) + E_S(R_2O)$ ' but ' $E_S(R_1) + E_S(R_2)$ ' since the data of Taft steric constants of  $R_1O$  are not available. <sup>e</sup>Strongly/Weakly basic pyridines. <sup>f</sup>Linear free energy relationship with X. <sup>g</sup>Biphasic concave upward free energy relationship with X.

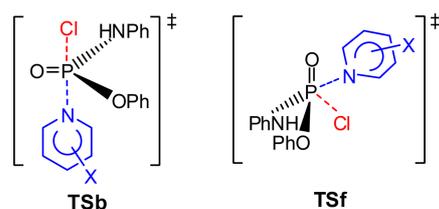


**Figure 4.** The plot of  $\log k_2$  vs  $\Sigma E_s$  for the reactions of **1-7** with  $C_5H_5N$  in MeCN at 35.0 °C. The number of the substrate and two ligands are displayed next to the corresponding point.

weakly basic pyridines for **5**; and (iii) considerably small values of 0.16-0.18 for **6**. The free energy relationships for substituent X variations in the X-pyridines are linear except **5**, showing biphasic concave upwards. The pyridinolyses of their P=S counterparts of dimethyl [(MeO)<sub>2</sub>P(=S)Cl],<sup>1a</sup> diethyl [(EtO)<sub>2</sub>P(=S)Cl],<sup>1a</sup> dipropyl [(PrO)<sub>2</sub>P(=S)Cl],<sup>11a</sup> dibutyl [(BuO)<sub>2</sub>P(=S)Cl],<sup>11b</sup> and Y-aryl phenyl [(PhO)(YC<sub>6</sub>H<sub>4</sub>O)P(=S)Cl]<sup>11c</sup> chlorothiophosphates all exhibited biphasic concave upward free energy relationships. The  $\beta_X$  values of the chlorothiophosphates are considerably large values of 1.02-1.50 with the strongly basic pyridines while relatively small values of 0.23-0.48 with the weakly basic pyridines,<sup>1a,11</sup> as obtained for **5**. A concerted S<sub>N</sub>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 ( $\beta_X = 1.02-1.50$ ) with the strongly basic pyridines to a backside attack (TSb;  $\beta_X = 0.23-0.48$ ) with the weakly basic pyridines for the pyridinolyses of **5** and chlorothiophosphates (Scheme 2).<sup>1a,d,11</sup> It is worthy of note that a frontside attack TSf yields greater magnitudes of  $\beta_X$  values compared to a backside attack.<sup>12</sup> A concerted mechanism with an early TS involving backside nucleophilic attack TSb towards the Cl leaving group was proposed on the basis of small negative CIC ( $\rho_{XY} = -0.15$ )<sup>13</sup> and small values of Brønsted coefficients ( $\beta_X = 0.16-0.18$ )<sup>14</sup> for the pyridinolysis of **6**.<sup>1c</sup> The S<sub>N</sub>2 reaction mechanism was proposed for the pyridinolyses of **1**, **2**, **3**, and **4** with both frontside TSf and backside attacks TSb, 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  $\beta_X$  ( $= 0.63, 0.73,$



**Scheme 2.** Backside attack TSb and frontside attack TSf for the pyridinolyses of chlorophosphates and chlorothiophosphates.



**Scheme 3.** Backside attack TSb and frontside attack TSf for the pyridinolysis of phenyl *N*-phenyl phosphoramidochloridate (**7**).

0.87, and 0.80 for **1**, **2**, **3**, and **4**, respectively) values.<sup>1a,b,c</sup>

In the present work of **7**, thus, the S<sub>N</sub>2 reaction mechanism is proposed with both frontside TSf and backside attacks TSb (Scheme 3), and the fraction of a frontside attack is somewhat greater than that of a backside attack, on the basis of the magnitude of  $\beta_X$  ( $= 0.75$ ) value.

In summary, the nucleophilic substitution reactions of phenyl *N*-phenyl phosphoramidochloridate (**7**) with X-pyridines are investigated kinetically in MeCN at 35.0 °C. The S<sub>N</sub>2 reaction mechanism is proposed with both frontside TSf and backside attacks TSb on the basis of the magnitude of  $\beta_X$  value. The steric effects of the two ligands on the pyridinolysis rates of the studied substrates are discussed based on the Taft eq. of  $\log k_2 = \delta \Sigma E_s + C$ .

## Experimental Section

**Materials.** Phenyl *N*-phenyl phosphoramidochloridate (99%), GR grade pyridines and HPLC grade acetonitrile (water content is less than 0.005%) were used for kinetic studies without further purification.

**Kinetic Procedure.** Rates were measured conductometrically at 35.0 °C.<sup>1</sup> The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. The pseudo-first-order rate constants,  $k_{\text{obsd}}$  were measured by curve fitting analysis in origin program with a large excess of pyridines, [substrate] =  $1 \times 10^{-3}$  M and [X-C<sub>5</sub>H<sub>4</sub>N] = (0.03-0.15) M. Second-order rate constants,  $k_2$ , were obtained from the slope of a plot of  $k_{\text{obsd}}$  vs [X-pyridine] with at least five concentrations of pyridine. The pseudo-first-order rate constant values ( $k_{\text{obsd}}$ ) were the average of three runs that were reproducible within  $\pm 3\%$ .

**Product Analysis.** Phenyl *N*-phenyl phosphoramidochloridate was reacted with excess pyridine, for more than 15 half-lives at 35.0 °C in MeCN. Acetonitrile was removed under reduced pressure. The product was isolated by adding ether and insoluble fraction was collected. The product was purified to remove excess pyridine by washing several times with ether. Analytical and spectroscopic data of the product gave the following results (see Supporting Information with activation parameters):

[(PhO)(NHPh)P(=O)NC<sub>5</sub>H<sub>5</sub>]<sup>+</sup>Cl<sup>-</sup>: Colorless liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.72 (1H, s, NH), 6.827.20 (10H, m, 2Ph), 7.73-7.77 (2H, t,  $J = 6.4$  Hz, pyridinium), 8.24 (1H, t,  $J = 8.0$  Hz, pyridinium), 8.71 (2H, d,  $J = 5.2$  Hz, pyridinium); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  118.76, 120.19, 122.36, 125.32, 126.61, 128.98, 129.17, 129.57, 129.59,

138.49, 141.77, 144.64 (C=C, aromatic);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  1.71 (1P, s, P=O); MS (ESI)  $m/z$  346 ( $\text{M}^+$ ).

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- The summation of steric constants of **7** is assumed as  $\Sigma E_{\text{S}} = -4.98 = [-2.48(E_{\text{S}} \text{ of Ph})] + [-2.50(E_{\text{S}} \text{ of PhH})]$ , taking into account ( $E_{\text{S}}$  of H) =  $-0.2$  with one hydrogen atom.
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- The magnitude of  $\rho_{\text{XY}}$  value is inversely proportional to the distance between X and Y through the reaction center, and the negative sign of  $\rho_{\text{XY}}$  implies that the reaction proceeds through a concerted mechanism, while a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate with the positive sign of  $\rho_{\text{XY}}$ . The value of  $\rho_{\text{XY}} = -0.15$  with **6** indicates a concerted mechanism and the long distance between X and Y. The value of  $\rho_{\text{XY}} = -0.7$  is a typical one for  $\text{S}_{\text{N}}2$  process.
- The small values of  $\beta_{\text{X}} = 0.16-0.18$  are consistent with the value of  $\rho_{\text{XY}} = -0.15$ , indicating very small extent of the degree of bond formation.