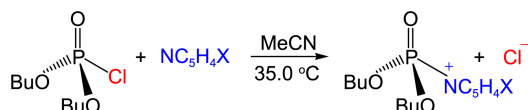


Pyridinolysis of Dibutyl Chlorophosphate in Acetonitrile<sup>†</sup>

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Received December 8, 2011, Accepted December 12, 2011**Key Words** : Phosphoryl transfer reaction, Pyridinolysis, Dibutyl chlorophosphate, Steric effect

Kinetics and mechanism of the phosphoryl and thiophosphoryl transfer reactions have been studied extensively by this lab: pyridinolyses,<sup>1</sup> anilinolyses,<sup>2</sup> and benzylaminolyses<sup>3</sup> of various substrates, and MO theoretical studies of the model compounds.<sup>4</sup> Herein, continuing the kinetic studies of the pyridinolyses of dimethyl [**1**: (MeO)<sub>2</sub>P(=O)Cl],<sup>1g</sup> diethyl [**2**: (EtO)<sub>2</sub>P(=O)Cl],<sup>1g</sup> diisopropyl [**4**: (i-PrO)<sub>2</sub>P(=O)Cl],<sup>1q</sup> Y-aryl phenyl [**5**: (PhO)(YC<sub>6</sub>H<sub>4</sub>O)P(=O)Cl],<sup>1a</sup> and bis(2,6-dimethylphenyl) [**6**: [2,6-(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>O]<sub>2</sub>P(=O)Cl]<sup>1t</sup> chlorophosphates, the nucleophilic substitution reactions of dibutyl chlorophosphate (**3**) with X-pyridines are investigated kinetically in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1) to gain further information into the reactivity and mechanism depending on the variation of the two ligands, R<sub>1</sub>O and R<sub>2</sub>O. The numbering of the substrates of **1-6** follows the sequence of the summation of the Taft's steric constants of the two ligands,<sup>5</sup> R<sub>1</sub> and R<sub>2</sub>: **6**[2,6-(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>O]<sub>2</sub> > **5**(PhO, YC<sub>6</sub>H<sub>4</sub>O) > **4**(i-PrO)<sub>2</sub> > **3**(BuO)<sub>2</sub> > **2**(EtO)<sub>2</sub> > **1**(MeO)<sub>2</sub>.



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 pyridinolysis of dibutyl chlorophosphate (**3**) in MeCN at 35.0 °C.**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  $\beta_X$  value was calculated by correlating  $\log k_2(\text{MeCN})$  with  $\text{p}K_{\text{a}}(\text{H}_2\text{O})$ ,<sup>6</sup> which was justified theoretically and experimentally.<sup>7</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  $\rho_X$  ( $= -4.39$ : Fig. 1) and positive  $\beta_X$  ( $= 0.80$ : Fig. 2) values.

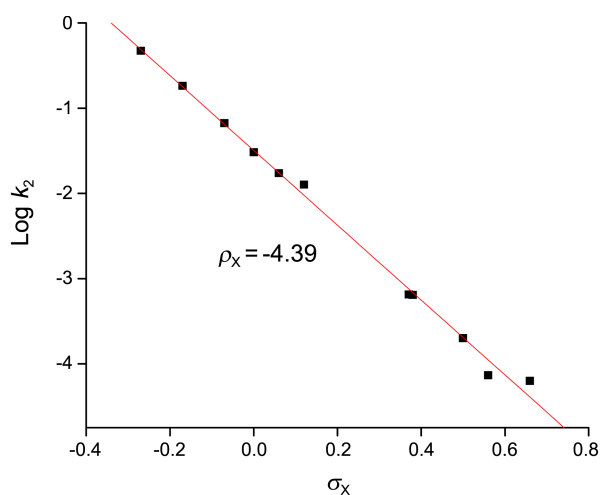
The second-order rate constants ( $k_2$ ) with unsubstituted pyridine (C<sub>5</sub>H<sub>5</sub>N) at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],<sup>8</sup> summations of the Taft's steric constants of R<sub>1</sub> and R<sub>2</sub> [ $\Sigma E_{\text{S}} = E_{\text{S}}(\text{R}_1) + E_{\text{S}}(\text{R}_2)$ ],<sup>5</sup> Brønsted coefficients ( $\beta_X$ ), cross-interaction constant (CIC;  $\rho_{\text{XY}}$ ),<sup>9</sup> and variation trends of the free energy relationships with X for the pyridinolyses of six (R<sub>1</sub>O)(R<sub>2</sub>O)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 **4** > **3** > **2** > **5** > **1** > **6**. On the other hand, when the steric effects of the two ligands (R<sub>1</sub>O and R<sub>2</sub>O) play an important role, the sequence of the rate should be **1** > **2** > **3** > **4** > **5** > **6**. The observed sequence of the pyridinolysis rates is **5** > **1** > **2** > **3** > **4** > **6**, giving the relative rates of 650(**5**) : 160(**1**) : 130(**2**) : 75(**3**) : 24(**4**) : 1(**6**). The pyridinolysis rate of **6** is exceptionally slow whereas that of **5** is exceptionally fast [note  $k_2(\mathbf{5} \text{ with } \text{Y} = \text{H})/k_2(\mathbf{6}) = 650$ ]. It is evident that the magnitude of the positive charge at the reaction center P atom does not play any role to determine the pyridinolysis rate.

At a glance, thus, it seems that the pyridinolysis rates are

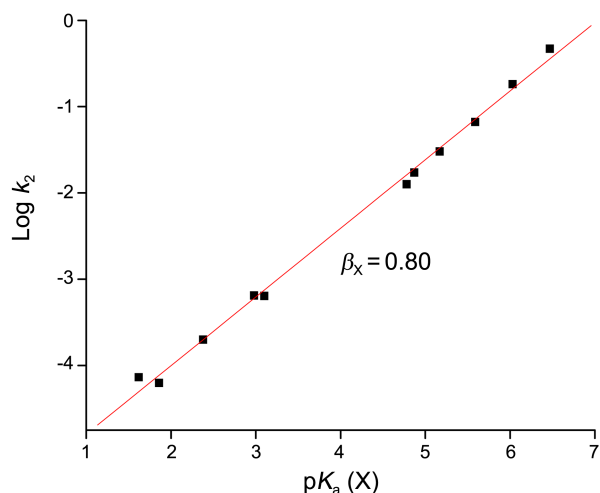
**Table 1.** Second-Order Rate Constants ( $k_2 \times 10^3/\text{M}^{-1} \text{s}^{-1}$ ) of the Reactions of Dibutyl Chlorophosphate (**3**) with XC<sub>5</sub>H<sub>4</sub>N in MeCN at 35.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2 \times 10^3$	469	183	66.8	30.4	17.2	12.6	0.647	0.640	0.200	0.0731	0.0630
	± 1	± 1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.002	± 0.001	± 0.001	± 0.0002	± 0.0002

<sup>†</sup>This paper is to commemorate Professor Kook Joe Shin's honourable retirement.



**Figure 1.** The Hammett plot ( $\log k_2$  vs  $\sigma_X$ ) of the reaction of dibutyl chlorophosphate (**3**) with X-pyridines in MeCN at 35.0 °C. The value of  $\rho_X$  is  $-4.39 \pm 0.10$  ( $r = 0.998$ ).



**Figure 2.** The Brønsted plot [ $\log k_2$  vs  $pK_a(X)$ ] of the reactions of dibutyl chlorophosphate (**3**) with X-pyridines in MeCN at 35.0 °C. The value of  $\beta_X$  is  $0.80 \pm 0.09$  ( $r = 0.998$ ).

inversely proportional to the summation of the steric constants of the two ligands ( $\Sigma E_S$ ),  $1 > 2 > 3 > 4 > 6$ , when excluding **5**. To examine into the steric effects of the two ligands on the pyridinolysis rates of the studied P=O and P=S systems involving chloride leaving group, the sensitivity coefficients of  $\delta$  are obtained from the Taft's eq. ( $\log k_2 = \delta \Sigma E_S + C$ )<sup>5</sup> for the pyridinolyses of (R<sub>1</sub>O)(R<sub>2</sub>O)P(=O)Cl-type chlorophosphates (**I**), (R<sub>1</sub>O)(R<sub>2</sub>O)P(=S)Cl-type chlorothiophosphates (**II**), R<sub>1</sub>R<sub>2</sub>P(=O)Cl-type phosphinic chlorides (**III**), and R<sub>1</sub>R<sub>2</sub>P(=S)Cl-type thiophosphinic chlorides (**IV**) in MeCN at 35.0 °C. In the case of **I** and **II**, it should be noted that the value of  $\Sigma E_S$  is not ' $E_S(R_1O) + E_S(R_2O)$ ' but ' $E_S(R_1) + E_S(R_2)$ ' since the data of Taft's steric constants of R<sub>i</sub>O are not available. Henceforth, for convenience to express the substrates, (R<sub>1</sub>O)(R<sub>2</sub>O)P(=A)Cl and R<sub>1</sub>R<sub>2</sub>P(=A)Cl are denoted as A(R<sub>1</sub>O,R<sub>2</sub>O) and A(R<sub>1</sub>,R<sub>2</sub>), respectively, where A = O or S. As seen in Table 3, the pyridinolysis rates of the P=O and P=S systems are partially dependent upon the steric effects of the two ligands: (i) in **I**, four substrates [O(MeO,MeO),<sup>1g</sup> O(EtO,EtO),<sup>1g</sup> O(BuO,BuO), and O(*i*-PrO,*i*-PrO)<sup>1q</sup>] semi-quantitatively follow the Taft's eq. with  $r = 0.904$ , excluding O(PhO,PhO)<sup>1a,10</sup> (ii) in **II**, four substrates [S(MeO,MeO),<sup>1g</sup> S(EtO,EtO),<sup>1g</sup> S(PrO,PrO)<sup>1x</sup> and S(PhO,PhO)<sup>1j</sup>] quantitatively follow the Taft's eq. with  $r = 0.996$  (*incidentally* good linearity), excluding S(EtO,PhO)<sup>1s</sup>; (iii) in **III**, four substrates [O(Me,Me),<sup>1h</sup> O(Et,Et),<sup>1i</sup> O(Me<sub>2</sub>N,Me<sub>2</sub>N),<sup>1w</sup> and O(cHex,cHex)<sup>1n</sup>] semi-quantitatively follow the Taft's eq. with  $r = 0.928$ , excluding O(Me,Ph)<sup>1m</sup> and O(Ph,Ph)<sup>1d</sup>; (iv) in **IV**, three substrates [S(Me,Me),<sup>1h</sup> S(Et,Et),<sup>1p</sup> and S(*i*-Pr,*i*-Pr)<sup>1v</sup>] qualitatively follow the Taft's eq. with  $r = 0.686$  (very bad linearity), excluding S(Ph,Ph).<sup>1d</sup> In general, the substrates with phenyl or phenoxy ligand do not follow the Taft's eq. These results suggest that the steric effects of the two ligands *sometimes* play an important role, qualitatively or quantitatively, to determine the pyridinolysis rate of chlorophosphates, chlorothiophosphates, phosphinic chlorides, and thiophosphinic chlorides.<sup>11</sup>

A concerted mechanism with an early TS involving

**Table 2.** Summary of the Second-Order Rate Constants ( $k_2 \times 10^3/M^{-1} s^{-1}$ ) with C<sub>5</sub>H<sub>5</sub>N at 35.0 °C, NBO Charges at the Reaction Center P Atom, Summations of the Taft's Steric Constants of R<sub>1</sub> and R<sub>2</sub> [ $\Sigma E_S = E_S(R_1) + E_S(R_2)$ ], Brønsted coefficients ( $\beta_X$ ), Cross-Interaction Constant ( $\rho_{XY}$ ), and Variation Trends of Free Energy Relationship with X for the Pyridinolyses (XC<sub>5</sub>H<sub>4</sub>N) of **1-6** in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-\Sigma E_S^e$	$\beta_X$	$\rho_{XY}$	Trend
<b>1:</b> (MeO) <sub>2</sub> P(=O)Cl	64.7	2.226	0.00	0.63 <sup>f</sup>	–	L <sup>l</sup>
<b>2:</b> (EtO) <sub>2</sub> P(=O)Cl	52.8	2.236	0.14	0.73 <sup>f</sup>	–	L
<b>3:</b> (BuO) <sub>2</sub> P(=O)Cl	30.4	2.239	0.78	0.80 <sup>f</sup>	–	L
<b>4:</b> ( <i>i</i> -PrO) <sub>2</sub> P(=O)Cl	9.60	2.269	0.94	1.05 <sup>g</sup> /0.39 <sup>b</sup>	–	V <sup>m</sup>
<b>5:</b> (PhO)(YC <sub>6</sub> H <sub>4</sub> O)P(=O)Cl	266 <sup>b</sup>	2.230 <sup>d</sup>	4.96	0.16-0.18 <sup>l</sup>	-0.15 <sup>l</sup>	L
<b>6:</b> [2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> O] <sub>2</sub> P(=O)Cl	0.407 <sup>c</sup>	2.214	> 4.96	0.86 <sup>l</sup> /-0.83 <sup>k</sup>	–	V

<sup>a</sup>Second-order rate constant with unsubstituted pyridine (X = H) at 35.0 °C. <sup>b</sup>Extrapolated value in the Arrhenius plot with kinetic data:  $k_2 = 37.1, 94.0,$  and  $135 \times 10^{-3} M^{-1} s^{-1}$  at 5.0, 15.0, and 25.0 °C, respectively, from ref. 1a. <sup>c</sup>Extrapolated value in the Arrhenius plot with kinetic data:  $k_2 = 0.688, 1.17,$  and  $1.83 \times 10^{-3} M^{-1} s^{-1}$  at 45.0, 55.0, and 65.0 °C, respectively. <sup>d</sup>The value with Y = H. <sup>e</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's steric constants of R<sub>i</sub>O are not available. <sup>f</sup>The value at 35.0 °C. <sup>g</sup>The value at 35.0 °C. X = (4-MeO, 4-Me, 3-Me, H, 3-Ph). <sup>h</sup>The value at 35.0 °C. X = (3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). <sup>i</sup>The value at 25.0 °C. <sup>j</sup>The value at 65.0 °C. X = (4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl). <sup>k</sup>The value at 65.0 °C. X = (3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). <sup>l</sup>Linear free energy relationship with X. <sup>m</sup>Biphasic concave upward free energy relationship with X.

**Table 3.** Examination into the Steric Effects of the Two ligands on the Pyridinolysis Rates of the P=O and P=S Systems Involving Cl Leaving Group in MeCN<sup>a</sup>

no	second-order rate constants ( $k_2 \times 10^3/\text{M}^{-1}\text{s}^{-1}$ ) of the P=O and P=S systems
I	semi-quantitatively tolerable; $64.7[\text{O}(\text{MeO},\text{MeO})] > 52.8[\text{O}(\text{EtO},\text{EtO})] > 30.4[\text{O}(\text{BuO},\text{BuO})] > 9.60[\text{O}(i\text{-PrO},i\text{-PrO})]$ ; $\delta = 0.72$ ( $r = 0.904$ ) excluding: $0.407[\text{O}(2,6\text{-Me}_2\text{C}_6\text{H}_3\text{O},2,6\text{-Me}_2\text{C}_6\text{H}_3\text{O})]$ , <sup>b</sup> $266[\text{O}(\text{PhO},\text{PhO})]$
II	quantitatively tolerable; $1.54[\text{S}(\text{MeO},\text{MeO})] > 1.19[\text{S}(\text{EtO},\text{EtO})] > 1.16[\text{S}(\text{PrO},\text{PrO})] > 0.137[\text{S}(\text{PhO},\text{PhO})]$ ; $\delta = 0.21$ ( $r = 0.996$ ) excluding: $0.333[\text{S}(\text{EtO},\text{PhO})]$
III	semi-quantitatively tolerable; $102,000[\text{O}(\text{Me},\text{Me})] > 127[\text{O}(\text{Et},\text{Et})] > 0.173[\text{O}(\text{Me}_2\text{N},\text{Me}_2\text{N})] > 0.0166[\text{O}(\text{cHex},\text{cHex})]$ ; $\delta = 3.85$ ( $r = 0.928$ ) excluding: $126,000[\text{O}(\text{Me},\text{Ph})]$ , $54.6[\text{O}(\text{Ph},\text{Ph})]$
IV	qualitatively tolerable; $0.744[\text{S}(\text{Me},\text{Me})] > 0.0960[\text{S}(\text{Et},\text{Et})] > 0.0760[\text{S}(i\text{-Pr},i\text{-Pr})]$ ; $\delta = 0.74$ ( $r = 0.686$ ) excluding: $1.83[\text{S}(\text{Ph},\text{Ph})]$

<sup>a</sup>The  $E_s$  value of NMe<sub>2</sub> is not available and that of *i*-Pr is introduced.  $E_s(\text{R}) = 0(\text{Me}); -0.07(\text{Et}); -0.36(\text{Bu}); -0.47(i\text{-Pr}); -0.79(\text{cHex}); -2.48(\text{Ph})$  from ref. 5. <sup>b</sup>See ref. 10.

backside nucleophilic attack TSb towards the Cl leaving group (Scheme 2) was proposed on the basis of small negative  $\rho_{XY}$  ( $\rho_{XY} = -0.15$ )<sup>12</sup> and small values of Brønsted coefficients ( $\beta_X = 0.16\text{--}0.18$ ) for the pyridinolysis of **5**.<sup>1a</sup> The S<sub>N</sub>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  $\beta_X$  ( $= 0.63$  and  $0.73$  for **1** and **2**, respectively) values.<sup>1g</sup> 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 ( $\beta_X = 1.05$ ) with the strongly basic pyridines to a backside attack (TSb;  $\beta_X = 0.39$ ) with the weakly basic pyridines for the pyridinolysis of **4**.<sup>14</sup> It is worthy of note that a frontside attack TSf yields greater magnitudes of  $\rho_X$  and  $\beta_X$  values compared to a backside attack.<sup>1c</sup> In the pyridinolysis of **6**, 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 and the positive  $\rho_X$  and negative  $\beta_X$  values are substantiated by an imbalance of the transition state.<sup>11</sup> In the present work, thus, the S<sub>N</sub>2 reaction mechanism is proposed with both frontside TSf and backside attacks TSb, and the fraction of a frontside attack is somewhat greater than that of a backside attack, on the basis of the magnitude of  $\beta_X$  ( $= 0.80$ ) value.

In summary, the nucleophilic substitution reactions of dibutyl chlorophosphate (**3**) 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 importance of the steric effects of the two ligands on the pyridinolysis rates of chlorophosphates, chlorothiophosphates, phosphinic chlorides, and thiophosphinic chlorides is discussed based on the Taft's eq. of  $\log k_2 = \sigma \sum E_s + C$ .

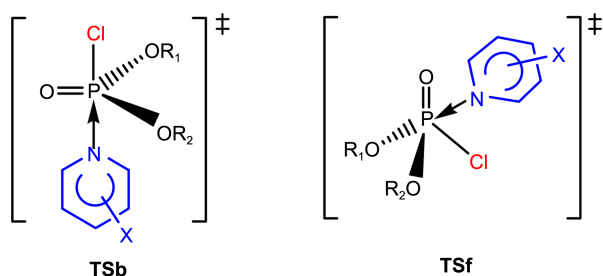
## Experimental Section

**Materials.** Dibutyl chlorophosphate (commercially available), 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. 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,  $[\text{substrate}] = 1 \times 10^{-3}$  M and  $[\text{XC}_5\text{H}_4\text{N}] = (0.03\text{--}0.15)$  M. Second-order rate constants,  $k_2$ , were obtained from the slope of a plot of  $k_{\text{obsd}}$  vs.  $[\text{X-pyridine}]$  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.** Dibutyl chlorophosphate 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 supplementary materials):

**[(BuO)<sub>2</sub>P(=O)NC<sub>5</sub>H<sub>5</sub>]<sup>+</sup>Cl<sup>-</sup>.** White solid; mp 40–41 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  0.85–0.90 (6H, m, 2CH<sub>3</sub>, Bu), 1.24–1.28 (4H, m, 2CH<sub>2</sub>, Bu), 1.82–1.93 (4H, m, 2CH<sub>2</sub>, Bu), 4.63–4.66 (4H, t,  $J = 7.6$  Hz, 2OCH<sub>2</sub>, BuO), 8.04–8.07 (2H, t,  $J = 6.4$  Hz, pyridinium), 8.57–8.60 (1H, t,  $J = 7.6$  Hz, pyridinium), 8.91–8.93 (2H, d,  $J = 5.6$  Hz, pyridinium); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.32 (CH<sub>3</sub>, Bu), 18.73 (CH<sub>2</sub>, Bu), 32.70 (CH<sub>2</sub>, Bu), 60.62 (OCH<sub>2</sub>, BuO), 127.23, 128.09, 141.87, 145.48, 145.90 (C=C, pyridinium); <sup>31</sup>P NMR (162 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  4.74 (s, 1P, P=O); MS (EI)

**Scheme 2.** Backside and frontside attack TS.

$m/z$  308 ( $M^+$ ).

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### References and Notes

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- There is no doubt that the pyridinolysis rate of **6** [O(2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>O,2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>O)] is exceptionally dependent upon the steric effects of the two ligands because of the four ortho-substituents. However, **6** is not considered to calculate  $\delta$  in Table 3 due to the lack of  $E_s$  for 2,6-dimethyl phenyl ligand. See ref. 1t for more detailed discussion.
- In contrast to the anilinolyses of the P=O and P=S systems in which the steric effects of the two ligands are the major factor to decide the anilinolysis rates, the pyridinolysis rates of the P=O and P=S systems are not predominantly *but partially, sometimes qualitatively or quantitatively*, dependent upon the steric effects of the two ligands. Further systematic works are essential to clarify the steric effects of the two ligands on the pyridinolysis rates of the P=O and P=S systems.
- The magnitude of  $\rho_{XY}$  value is inversely proportional to the distance between X and Y through the reaction center, and the negative sign of  $\rho_{XY}$  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  $\rho_{XY}$ . The value of  $\rho_{XY} = -0.7$  is a typical one for  $S_N2$  process.