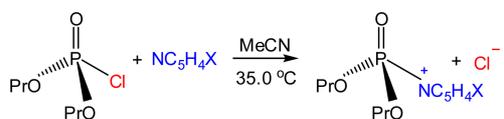


## Pyridinolysis of Dipropyl Chlorophosphate in Acetonitrile

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Received February 15, 2012, Accepted June 30, 2012**Key Words** : Phosphoryl transfer reaction, Pyridinolysis, Dipropyl chlorophosphate, Steric effect

Continuing the kinetic studies on the pyridinolyses of dimethyl **1**: (MeO)<sub>2</sub>P(=O)Cl,<sup>1a</sup> diethyl **2**: (EtO)<sub>2</sub>P(=O)Cl,<sup>1a</sup> dibutyl **4**: (BuO)<sub>2</sub>P(=O)Cl,<sup>1b</sup> diisopropyl **5**: (*i*-PrO)<sub>2</sub>P(=O)Cl,<sup>1c</sup> and Y-aryl phenyl **6**: (PhO)(YC<sub>6</sub>H<sub>4</sub>O)P(=O)Cl<sup>1d</sup> chlorophosphates, the nucleophilic substitution reactions of dipropyl chlorophosphate (**3**) 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, 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 steric constants of the two ligands,<sup>2</sup> R<sub>1</sub> and R<sub>2</sub>: **6**(PhO,YC<sub>6</sub>H<sub>4</sub>O) > **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>.



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 dipropyl chlorophosphate (**3**) in MeCN at 35.0 °C.

## Results and Discussion

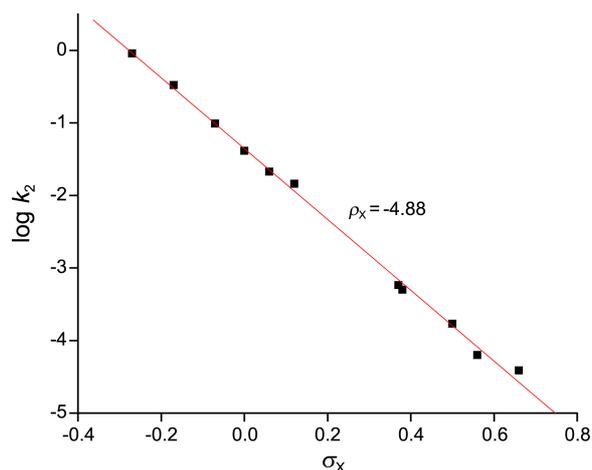
The reactions were carried out under pseudo-first-order conditions with a large excess of pyridine. The observed pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) for all the reactions obeyed Eq. (1) with negligible  $k_0$  ( $\approx 0$ ) in MeCN. The clean second-order rate constants were determined 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 sum-

marized in Table 1. The Brönsted  $\beta_X$  value was calculated by correlating  $\log k_2(\text{MeCN})$  with  $\text{p}K_a(\text{H}_2\text{O})$ ,<sup>3</sup> which was justified theoretically and experimentally.<sup>4</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  $\rho_X$  ( $= -4.88$ ; Fig. 1) and positive  $\beta_X$  ( $= 0.87$ ; Fig. 2) values.

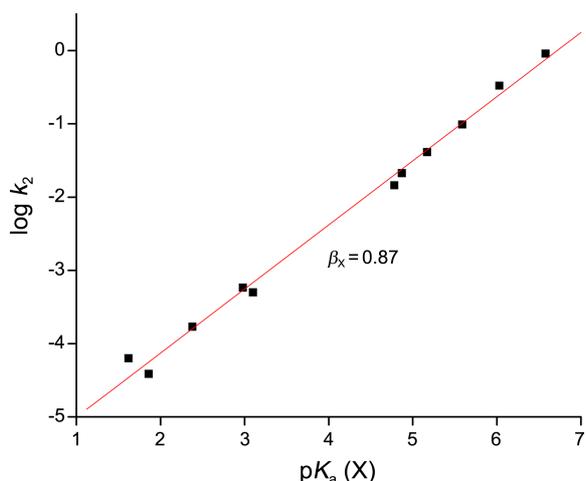
The second-order rate constants ( $k_2$ ) with unsubstituted pyridine (C<sub>5</sub>H<sub>5</sub>N) at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],<sup>5</sup> summations of the Taft steric constants of R<sub>1</sub> and R<sub>2</sub> [ $\sum E_s = E_s(\text{R}_1) + E_s(\text{R}_2)$ ],<sup>2</sup> Brönsted coefficients ( $\beta_X$ ), cross-interaction constant (CIC;  $\rho_{XY}$ ),<sup>6</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.



**Figure 1.** The Hammett plot ( $\log k_2$  vs  $\sigma_X$ ) of the reaction of dipropyl chlorophosphate (**3**) with X-pyridines in MeCN at 35.0 °C. The value of  $\rho_X$  is  $-4.88 \pm 0.09$  ( $r = 0.999$ ).

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

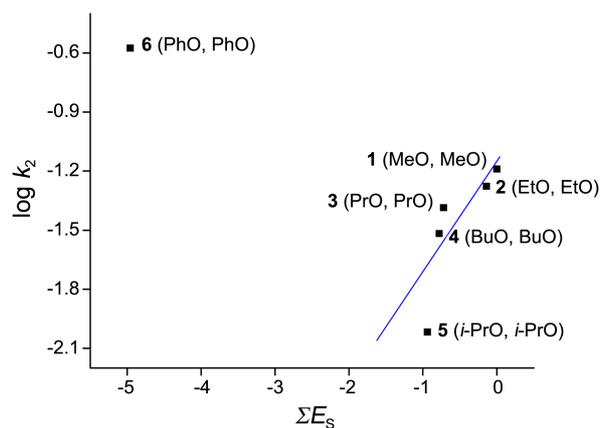
X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2$	909	332	97.7	41.2	21.3 ±	14.5	0.580	0.503 ±	0.170	0.0631	0.0387
$\times 10^3$	± 2	± 1	± 0.2	± 0.1	0.1	± 0.1	± 0.001	0.001	± 0.001	± 0.0001	± 0.0001



**Figure 2.** The Brønsted plot [ $\log k_2$  vs  $pK_a(X)$ ] of the reactions of dipropyl chlorophosphate (**3**) with X-pyridines in MeCN at 35.0 °C. The value of  $\beta_X$  is  $0.87 \pm 0.13$  ( $r = 0.997$ ).

There is no correlation between the pyridinolysis rate and the magnitude of the positive charge of the reaction center P atom in the substrate, suggesting that the inductive effects of the two ligands do not play any role to determine the pyridinolysis rate.

At a glance, the pyridinolysis rates are inversely proportional to the summation of the steric constants of the two ligands ( $\Sigma E_s$ ),  $1 > 2 > 3 > 4 > 5$ , when excluding **6** (with Y = H). To examine into the steric effects of the two ligands on the pyridinolysis rates of the studied P=O systems, the sensitivity coefficient of  $\delta$  ( $= 0.64$  with  $r = 0.816$ ) are obtained from the Taft eq. ( $\log k_2 = \delta \Sigma E_s + C$ ) as shown in Figure 3.<sup>2</sup> It should be noted that the value of  $\Sigma E_s$  is not ' $E_s(R_1O) + E_s(R_2O)$ ' but ' $E_s(R_1) + E_s(R_2)$ ' since the data of Taft steric constants of R<sub>i</sub>O are not available:  $E_s(R) = 0(\text{Me})$ ;  $-0.07(\text{Et})$ ;  $-0.36(\text{Pr})$ ;  $-0.39(\text{Bu})$ ;  $-0.47(i\text{-Pr})$ ;  $-2.48(\text{Ph})$ .<sup>2</sup> The pyridinolysis rate of **6** (with Y = H) shows exceptionally great positive deviation from the slope. The dependence of the rate upon the steric effects of the two ligands is not quantitative but qualitative. In the case of the chlorothiophosphates [(R<sub>1</sub>O)(R<sub>2</sub>O)P(=S)Cl], the pyridinolysis rates are



**Figure 3.** The plot of  $\log k_2$  vs  $\Sigma E_s$  for the reactions of **1-6** 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.

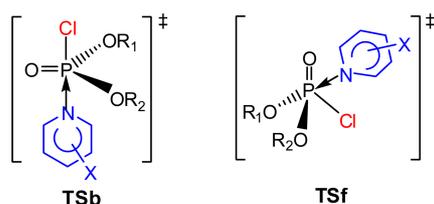
also semi-quantitatively correlated with the steric effects of the two ligands.<sup>1a,7</sup> Figure R1<sup>7</sup> can be explained in two ways: (i) diphenyl chlorothiophosphate [(PhO)<sub>2</sub>P(=S)Cl]<sup>7a</sup> shows exceptionally great positive deviation from the slope, the same as observed in the chlorophosphates; or (ii) phenyl ethyl chlorothiophosphate [(EtO)(PhO)P(=S)Cl]<sup>7b</sup> shows negative deviation from the slope. The  $\delta$  value with the chlorophosphates is greater than that with the chlorothiophosphates, indicating that the steric effects of the two ligands on the pyridinolysis rates of chlorophosphates are greater than those of chlorothiophosphates.

The free energy relationships for substituent X variations in the nucleophiles are linear with **1**, **2**, **3**, **5**, and **6** while biphasic concave upwards with **4**. The  $\beta_X$  ( $= 0.16\text{--}0.18$ ) values of **6** are exceptionally small and that ( $\beta_X = 0.39$ ) of **5** with the weakly basic pyridines is relatively small. A concerted mechanism with an early TS involving backside nucleophilic attack TS<sub>b</sub> towards the Cl leaving group (Scheme 2) was proposed on the basis of small negative CIC ( $\rho_{XY} = -0.15$ )<sup>8</sup> and small values of Brønsted coefficients ( $\beta_X = 0.16\text{--}0.18$ ) for the pyridinolysis of **6**.<sup>1d</sup> The S<sub>N</sub>2 reaction mechanism was proposed for the pyridinolyses of **1**, **2**, and **4** with both frontside TS<sub>f</sub> and backside attacks TS<sub>b</sub> (Scheme

**Table 2.** Summary of the Second-Order Rate Constants ( $k_2 \times 10^3/\text{M}^{-1} \text{s}^{-1}$ ) with  $C_5H_5N$  at 35.0 °C, NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants of R<sub>1</sub> and R<sub>2</sub> [ $\Sigma E_s = E_s(R_1) + E_s(R_2)$ ], Brønsted coefficients ( $\beta_X$ ), CIC ( $\rho_{XY}$ ), and Variation Trends of Free Energy Relationship with X for the Pyridinolyses (XC<sub>5</sub>H<sub>4</sub>N) of **1-6** in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-\Sigma E_s^d$	$\beta_X$	$\rho_{XY}$	Trend
<b>1:</b> (MeO) <sub>2</sub> P(=O)Cl	64.7	2.226	0.00	0.63	–	L <sup>g</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 <sup>e</sup> /0.39 <sup>f</sup>	–	V <sup>h</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>c</sup>	4.96 <sup>c</sup>	0.16–0.18	–0.15	L

<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  $135 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  at 5.0, 15.0, and 25.0 °C, respectively, from ref. 1a. <sup>c</sup>The value with Y = H. <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<sub>i</sub>O are not available. <sup>e</sup>Strongly basic pyridines. <sup>f</sup>Weakly basic pyridines. <sup>g</sup>Linear free energy relationship with X. <sup>h</sup>Biphasic concave upward free energy relationship with X.



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

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, 0.73, and 0.80 for **1**, **2**, and **4**, respectively) values.<sup>1a,b</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>1c</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>9</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  $\beta_X$  (= 0.87) value.

In summary, the nucleophilic substitution reactions of dipropyl 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 is discussed based on the Taft eq. of  $\log k_2 = \delta \Sigma E_S + C$ .

### Experimental Section

**Materials.** Dipropyl chlorophosphate (97%), 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, [substrate] =  $1 \times 10^{-3}$  M and [XC<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.** Dipropyl chlorophosphate was reacted with excess pyridine, for more than 15 half-lives at 35.0 °C in MeCN. Acetonitrile was removed under reduced pressure.

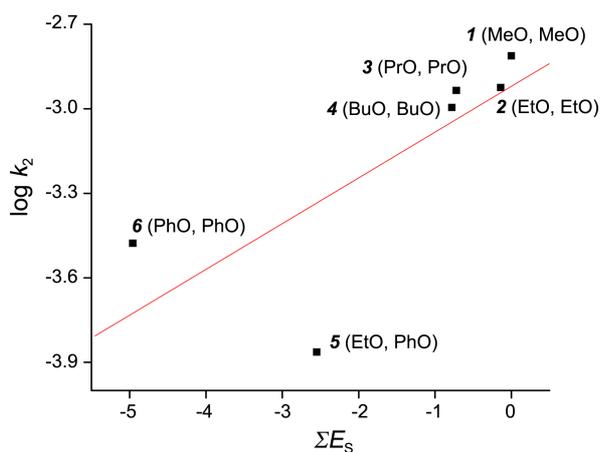
The product was isolated by adding ether and insoluble fraction was collected. The product was purified to remove excess pyridine by washing several times with ether. Analytical and spectroscopic data of the product gave the following results (see Supporting Information with activation parameters):

[(PrO)<sub>2</sub>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>)  $\delta$  0.860.99 (6H, m, 2CH<sub>3</sub>, Pr), 1.64-1.78 (4H, m, 2CH<sub>2</sub>, Pr), 4.07-4.18 (4H, m, 2OCH<sub>2</sub>, PrO), 7.92-7.96 (2H, t,  $J = 7.6$  Hz, pyridinium), 8.41-8.45 (1H, t,  $J = 8.4$  Hz, pyridinium), 8.90-8.92 (2H, d,  $J = 6.0$  Hz, pyridinium); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  9.82 (CH<sub>3</sub>, Pr), 18.40, 23.15-23.48 (CH<sub>2</sub>, Pr), 70.54, 71.19 (OCH<sub>2</sub>, PrO), 103.54, 126.83, 141.79 (C=C, pyridinium); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>)  $\delta$  -7.52 (s, 1P, P=O); MS (ESI)  $m/z$  279 (M<sup>+</sup>).

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### References and Notes

- (a) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, H. W. *J. Phys. Org. Chem.* **2010**, *23*, 1022. (b) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 1055. (c) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3505. (d) Guha, A. K.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 12.
- (a) Taft, R. W. *Steric Effect in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 3. (b) Exner, O. *Correlation Analysis in Chemistry: Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; p 439.
- The pK<sub>a</sub>(H<sub>2</sub>O) 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. (c) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906.
- (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. (c) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099. (d) Ritchie, C. D. *Solute Solvent Interactions*; Marcel-Dekker: New York, 1969; p 228. (e) Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834.
- Hehre, W. J.; Random, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; Chapter 4.
- (a) Lee, I. *Chem. Soc. Rev.* **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57. (c) Lee, I.; Lee, H. W. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1529.
- (a) Hoque, M. E. U.; Dey, S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1138. (b) Adhikary, K. K.; Lumbiny, B. J.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3947. (c) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 325. (d) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 1085. Fig. R1 shows semi-quantitatively linear correlation between the pyridinolysis rates and steric effects of the two ligands for the reactions of chlorothiophosphates (**I-6**) with C<sub>5</sub>H<sub>5</sub>N in MeCN at 35.0 °C, giving the sensitivity coefficients of  $\delta = 0.16$  ( $r = 0.754$ ) with six substrates of **I-6**,  $\delta = 0.41$  ( $r = 0.973$ ) with five substrates of **I-5**, and  $\delta = 0.12$  ( $r = 0.989$ ) with five substrates of **I**, **2**, **3**, **4**, and **6**.



**Figure R1.** The plot of  $\log k_2$  vs  $\Sigma E_s$  for the reactions of six chlorothiophosphates  $[(R_1O)(R_2O)P(=S)Cl]$  with  $C_5H_5N$  in MeCN at 35.0 °C. The two ligands of  $R_1O$  and  $R_2O$  are displayed next to the corresponding point.

8. 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 (or a stepwise mechanism with a rate-limiting bond formation), 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.

9. Adhikary, K. K.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 1135.