Pyridinolysis of Dibutyl Chlorophosphate in Acetonitrile

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Kinetics and mechanism of the phosphoryl and thiophosphoryl transfer reactions have been studied extensively by this lab: pyridinolyses, anilinolyses, and benzylaminolyses of various substrates, and MO theoretical studies of the model compounds. Herein, continuing the kinetic studies of the pyridinolyses of dimethyl [1: (MeO)2P(=O)Cl],[a] diethyl [2: (EtO)2P(=O)Cl],[b] diisopropyl [4: (i-PrO)2P(=O)Cl],[c] 1Y-aryl phenyl [5: (PhO)(YC6H4O)P(=O)Cl],[d] and bis(2,6-dimethylphenyl) [6: [2,6-(CH3)2C6H4O]2P(=O)Cl] chlorophosphates, the nucleophilic substitution reactions of dibutyl chlorophosphate (3) with X-pyridines are investigated kinetically in acetonitrile (MeCN) at 35.0 ± 1 °C (Scheme 1) to gain further information into the reactivity and mechanism depending on the variation of the two ligands, R1 and R2. The numbering of the substrates of 1-6 follows the sequence of the summation of the Taft’s steric constants of the two ligands, R1 and R2: 6 [2,6-(CH3)2C6H4O] > 5 [PhO,YC6H4O] > 4 (i-PrO)2 > 3 (BuO)2 > 2 (EtO)2 > 1 (MeO)2.

\[ X = 4-\text{MeO}, 4-\text{Me}, 3-\text{Me}, \text{H}, 3-\text{Ph}, 3-\text{MeO}, 3-\text{Cl}, 3-\text{Ac}, 4-\text{Ac}, 3-\text{CN}, 4-\text{CN} \]

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 \( k_0 \) 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.

\[ k_{\text{obsd}} = k_0 + k_2 [\text{XC}_2\text{H}_2\text{N}] \] (1)

The second-order rate constants \( k_2 \) (M\(^{-1}\) s\(^{-1}\)) are summarized in Table 1. The Brönsted \( \beta_X \) value was calculated by correlating log \( k_2 \) (MeCN) with \( pK_a(\text{H}_2\text{O}) \) which was justified theoretically and experimentally. 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 \( \rho_{\text{NX}} \) (\( \approx -4.39 \)) of Fig. 1 and positive \( \beta_X \) (\( = 0.80 \)) of Fig. 2 values.

The second-order rate constants \( k_2 \) with unsubstituted pyridine (C\(_2\)H\(_2\)N) at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the gas phase \( \{\text{B3LYP/6-311+G(d,p) level of theory}\} \), summations of the Taft’s steric constants of the two ligands, \( R_1 \) and \( R_2 \), \( \Sigma E_8 = E_8(R_1) + E_8(R_2) \), Brönsted coefficients \( \beta_X \), cross-interaction constant (CIC; \( \rho_{\text{CIC}} \)), and variation trends of the free energy relationships with \( X \) for the pyridinolyses of six \( (\text{R}_1\text{O})\text{R}_2\text{OP}(=\text{O})\text{Cl} \)-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 (R1 and R2) 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 \( k_2(5) \) with \( Y = \text{H} \)/\( k_2(6) \) = 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>
<thead>
<tr>
<th>( k_2 \times 10^3 )</th>
<th>4-MeO</th>
<th>4-Me</th>
<th>3-Me</th>
<th>H</th>
<th>3-Ph</th>
<th>3-MeO</th>
<th>3-Cl</th>
<th>3-Ac</th>
<th>4-Ac</th>
<th>3-CN</th>
<th>4-CN</th>
</tr>
</thead>
<tbody>
<tr>
<td>469</td>
<td>183</td>
<td>66.8</td>
<td>30.4</td>
<td>17.2</td>
<td>12.6</td>
<td>0.647</td>
<td>0.640</td>
<td>0.200</td>
<td>0.0731</td>
<td>0.0630</td>
<td></td>
</tr>
<tr>
<td>±1</td>
<td>±1</td>
<td>±0.1</td>
<td>±0.1</td>
<td>±0.1</td>
<td>±0.1</td>
<td>±0.002</td>
<td>±0.001</td>
<td>±0.001</td>
<td>±0.0002</td>
<td>±0.0002</td>
<td></td>
</tr>
</tbody>
</table>

*This paper is to commemorate Professor Kook Joe Shin’s honourable retirement.

Notes

http://dx.doi.org/10.5012/bkcs.2012.33.3.1055
The value of \( \rho_X \) is \(-4.39 \pm 0.10 \) (\( r = 0.998 \)).

The Brönsted plot \( [\log k_2 \text{ vs } \sigma_X] \) of the reaction of dibutyl chlorophosphate (3) with X-pyridines in MeCN at 35.0 °C. The value of \( \beta_X \) is 0.80 ± 0.09 (\( r = 0.998 \)).

The Hamnett plot \( (\log k_2 \text{ vs } \rho_X) \) of the reaction of dibutyl chlorophosphate (3) with X-pyridines in MeCN at 35.0 °C.

The value of \( \rho_X \) is \( -4.39 \pm 0.10 \) (\( r = 0.998 \)).

The value at 35.0 °C, 65.0 °C, and 25.0 °C, respectively, from ref. 1a.

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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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>second-order rate constants ((k_2 \times 10^{4}\text{M}^{-1}\text{s}^{-1})) of the P=O and P=S systems</th>
</tr>
</thead>
</table>
| I        | semi-quantitatively tolerable; 64.7[O(MeO,MeO)] \(\geq 52.8[O(\text{EtO},\text{EtO})] \geq 30.4[O(\text{BuO},\text{BuO})] \geq 9.60[O(i-\text{PrO},i-\text{PrO})]; \delta = 0.72 (r = 0.904)
|          | excluding: 0.407[O(2.6-MeC_{6}H_{4}O,2.6-MeC_{6}H_{4}O)]; 0.26[O(\text{PhO},\text{PhO})] |
| II       | quantitatively tolerable; 1.54[S(MeO,MeO)] \(\geq 1.19[S(\text{EtO},\text{EtO})] \geq 1.16[S(\text{PrO},\text{PrO})] \geq 1.037[S(\text{PhO},\text{PhO})]; \delta = 0.21 (r = 0.996)
|          | excluding: 0.333[S(\text{PhO},\text{PhO})] |
| III      | semi-quantitatively tolerable; 0.102000[O(\text{Me},\text{Me})] \(\geq 0.127000[O(\text{Et},\text{Et})] \geq 0.173000[O(\text{Me},N,\text{Me})] \geq 0.106600[O(\text{Hex},\text{Hex})]; \delta = 3.85 (r = 0.928)
|          | excluding: 126,000[O(\text{Me},\text{Ph}), 54.6[O(\text{Ph},\text{Ph})] |
| IV       | qualitatively tolerable; 0.74[S(Me,Me)] \(\geq 0.0960[S(\text{Et},\text{Et})] \geq 0.0760[S(i-\text{Pr},i-\text{Pr})]; \delta = 0.74 (r = 0.686)
|          | excluding: 1.83[S(\text{Ph},\text{Ph})] |

\*The \(E_5\) value of NMe2 is not available and that of i-Pr is introduced. \(E_0(R) = 0(\text{Me}) - 0.07(\text{Et}) - 0.36(\text{Bu}) - 0.47(i-\text{Pr}) - 0.79(\text{cHex}) - 2.48 (\text{Ph})\) from ref. 5. \*See ref. 10.

backside nucleophilic attack TSb towards the Cl leaving group (Scheme 2) was proposed on the basis of small negative CIC (\(\rho_X = -0.15\)) and small values of Brønsted coefficients (\(\beta_X = 0.16-0.18\)) for the pyridinolysis of 5. The \(S_{12}\) reaction mechanism was proposed for the pyridinolyses of 1-5, 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 \(\beta_X (= 0.63 \text{and} 0.73 \text{for} 1 \text{and} 2, \text{respectively})\) values. A concerted \(S_{12}\) 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. It is worthy of note that a frontside attack TSf yields greater magnitudes 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 \(k_2 = \sigma E_S + C\). 

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, [substrate] \(= 1 \times 10^{-3}\) M and [X:CH:HN] \(= 0.03-0.15\) M. Second-order rate constants, \(k_2\) were obtained from the slope of a plot of \(k_{\text{obsd}} vs. [X-\text{pyridine}]\) with at least five concentrations of pyridine. The pseudo-first-order rate constant values \(k_{\text{bd}}\) 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 in MeCN. Acetonitrile was removed under reduced pressure. 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:CH:HN] \(= 0.03-0.15\) M. Second-order rate constants, \(k_2\) were obtained from the slope of a plot of \(k_{\text{obsd}} vs. [X-\text{pyridine}]\) with at least five concentrations of pyridine. The pseudo-first-order rate constant values \(k_{\text{bd}}\) were the average of three runs that were reproducible within \(\pm 3\%\).
m/z 308 (M+).}

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

References and Notes


5. The δ value is inversely proportional to the steric effects of the two ligands because of the four ortho-substituents. However, δ is not considered to calculate δ in Table 3 due to the lack of δ for 2,6-dimethyl phenyl ligand. See ref. 1t for more detailed discussion.

6. 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 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.

7. The magnitude of ρXY value is inversely proportional to the distance between X and Y through the reaction center, and the negative sign of ρXY 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 ρXY. The value of ρXY = −0.7 is a typical one for S2 process.