Pyridinolysis of Phenyl N-Phenyl Phosphoramidochloridate in Acetonitrile

Md. Ehtesham Ul Hoque and Hai Whang Lee*

Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr

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Kinetics and mechanism of the aminolyses for various substrates have been studied extensively by this lab. The studied substrates are dominantly \((R_1)(RO)\)(POCl\(_2\)) type where \(R_1\) and \(R_2\) are alky1 and/or phenyl (aryl). Herein, the nucleophilic substitution reactions of phenyl N-phenyl phosphoramidochloridate \((7)\), involving anilino \((C_6H_4NH)\) 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 \([1:\ (MeO)_2]PF(=O)Cl\), diethyl \([2: (EtO)_2]PF(=O)Cl\), dipropyl \([3: (PrO)_2]PF(=O)Cl\), dibutyl \([4: (BuO)_2]PF(=O)Cl\), diisopropyl \([5: (i-PrO)_2]PF(=O)Cl\) and Y-aryl phenyl \([6: (PhO)(YC_6H_4)]PF(=O)Cl\) chlorophosphates. The numbering of the substrates of \(1-6\) follows the sequence of the summation of the Taft steric constants of the two ligands, \(R_1\) and \(R_2\): \(6[Y=H; (PhO)_2] > 5(i-PrO)_2 > 4(BuO)_2 > 3(PrO)_2 > 2(EtO)_2 > 1(MeO)_2\). The magnitude of \(E_\beta(PhNH)\) in 7 must be larger than that of \(E_\beta(PhO)\) 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. 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 \((\Delta\delta_{3S} = 0.36)\) is smaller than \(6\) \((\Delta\delta_{3S} = 0.40)\).

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.

\[
k_{\text{obsd}} = k_0 + k_2[XC_6H_4N] \quad (1)
\]

The second-order rate constants \((k_2 (M^{-1} s^{-1}))\) are summarized in Table 1. The Brønsted \(pK_a\) value was calculated by correlating \(log\ k_2(\text{MeCN})\) 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 \(p_X = -4.15\) (Fig. 2) and positive \(\beta_X = 0.75\) (Fig. 3) values.

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

**Table 1. Second-Order Rate Constants \((k_2 \times 10^3 M^{-1} s^{-1})\) of the Reactions of Phenyl N-Phenyl Phosphoramidochloridate \((7)\) with XC\(_6\)H\(_4\)N in MeCN at 35.0 °C**

<table>
<thead>
<tr>
<th>X</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>
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<tbody>
<tr>
<td>(k_2)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(\times 10^3)</td>
<td>\pm 1</td>
<td>\pm 0.1</td>
<td>\pm 0.1</td>
<td>\pm 0.01</td>
<td>\pm 0.01</td>
<td>\pm 0.001</td>
<td>\pm 0.001</td>
<td>\pm 0.002</td>
<td>\pm 0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Figure 1.** The B3LYP/6-311+G(d,p) geometries of phenyl N-phenyl phosphoramidochloridate \((7)\) in the gas phase.
Trends of Free Energy Relationship with X for the Pyridinolyses (XC
Atom, Summations of the Taft Steric Constants of R

Table 2. Summary of the Second-Order Rate Constants ($k_2 \times 10^5$ M$^{-1}$ s$^{-1}$) with CH$_2$N at 35.0 °C, NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants of R$_1$ and R$_2$ [$\Sigma E_X = E_0(R_1) + E_0(R_2)$], Brönsted coefficients ($\beta_X$), CIC ($\rho_{CV}$), and Variation Trends of Free Energy Relationship with X for the Pyridinolyses (XCH$_2$N) of 1-7 in MeCN

$^a$Second-order rate constant with unsubstituted pyridine (X = H) in MeCN at 35.0 °C. $^b$Extrapolated value. $^c$Note that the value of $\Sigma E_X$ is not $E_0(R_1)$ + $E_0(R_2)$ but $E_0(R_1) + E_0(R_2)$ since the data of Taft steric constants of R$_2$ are not available. $^d$Strongly/Weakly basic pyridines. $^e$Linear free energy relationship with X. $^f$Biphasic concave upward free energy relationship with X.
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 for 6, showing biphasic concave upwards. The pyridinolyses of their P=S counterparts of dimethyl [(MeO)2P(=S)Cl]1a,1e diethyl [(EtO)2P(=S)Cl]1a dipropyl [(PrO)2P(=S)Cl]1a dibutyl [(BuO)2P(=S)Cl]1e and Y-aryl phosphoramidochloridates all exhibited biphasic concave upward free energy relationships. The βk 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,1a,1l as obtained for 5. A concerted S2 reaction mechanism was proposed for the reactions of 1-7 with C6H5N in MeCN at 35.0 ºC. The number of the substrate and two ligands are displayed next to the corresponding point.

In the present work of 7, thus, the S2 reaction mechanism is proposed with both frontside TSf and backside attacks TSb (Scheme 3), and the fraction of a backside attack is somewhat greater than that of a frontside attack, on the basis of the magnitude of βk (= 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 ºC. The S2 reaction mechanism is proposed with both frontside TSf and backside attacks TSb on the basis of the magnitude of βk 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 k2 = δΣE5 + 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 ºC.1 The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. The pseudo-first-order rate constants, kobsd were measured by curve fitting analysis in origin program with a large excess of pyridines, [substrate] = 1 × 10-3 M and [XC6H5N] = (0.03-0.15) M. Second-order rate constants, k2, were obtained from the slope of a plot of kobsd vs [X-pyridine] with at least five concentrations of pyridine. The pseudo-first-order rate constant values (kobsd) were the average of three runs that were reproducible within ± 3%.

Product Analysis. Phenyl N-phenyl phosphoramidochloridate was reacted with excess pyridine, for more than 15 half-lives at 35.0 ºC in MeCN. Acetonitrile was removed under reduced pressure. The product was isolated by adding ether and insoluble fraction was collected. The product was isolated by adding ether. Analytical and spectroscopic data of the product were measured by curve fitting analysis in origin program with a large excess of pyridines, [substrate] = 1 × 10-3 M and [XC6H5N] = (0.03-0.15) M. Second-order rate constants, k2, were obtained from the slope of a plot of kobsd vs [X-pyridine] with at least five concentrations of pyridine. The pseudo-first-order rate constant values (kobsd) were the average of three runs that were reproducible within ± 3%.

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).

138.49, 141.77, 144.64 (C=C, aromatic); 31P NMR (162 MHz, CDCl₃) δ 1.71 (1P, s, P=O); MS (ESI) m/z 346 (M⁺).

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References and Notes


10. The summation of steric constants of 7 is assumed as ΣE = –4.98 = [–2.48(EPh) + (–2.50(EPhH)], taking into account (EPh of H) = –0.2 with one hydrogen atom.


13. 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 = –0.15 with 6 indicates a concerted mechanism and the long distance between X and Y. The value of ρXY = –0.7 is a typical one for 5,6,2 process.

14. The small values of β = 0.16-0.18 are consistent with the value of ρXY = –0.15, indicating very small extent of the degree of bond formation.