Pyridinolysis of Diethyl Phosphinic Chloride in Acetonitrile

Nilay Kumar Dey, Chan Kyung Kim,* and Hai Whang Lee*

Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr
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Nucleophilic substitution on P=O (and P=S) center is not only important in biochemistry and is also extensive in synthesis and organometallic chemistry. The authors reported various types of phosphoryl transfer reactions to clarify the mechanism. Herein, the reactions of diethyl phosphinic chloride (2O) with substituted pyridines are investigated kinetically in acetonitrile at 45.0 ± 0.1 °C to gain further information of mechanism. The pyridinolyses of eleven R1R2P(=O or S)Cl-type substrates in MeCN (eq 1) are reviewed to obtain systematic information on phosphoryl transfer reactions to clarify the mechanism. The kinetic results were justified theoretically and experimentally. Both the Hammett (\( \rho_X \)) and Brönsted (\( k_2 \)) plots are linear with \( \rho_X = -2.52 \pm 0.08 \) (\( r = 0.996 \)) and \( \beta_X = 0.45 \pm 0.02 \) (\( r = 0.994 \)).

Table 1 shows the summations of inductive effects of the two ligands \( \sum \sigma = \sigma(R_1) + \sigma(R_2) \), natural bond order (NBO) charges on the P atom reaction center in the gas phase [B3LYP/6-311+G(d,p) level of theory], \( \beta \) summations of steric parameters of the two ligands \( \sum E_S = E_S(R_1) + E_S(R_2) \), second-order rate constants \( k_2 \) at 35.0 °C, and Brönsted coefficients \( \beta_X \) and cross-interaction constants (CICs; \( \rho_X \)) for the pyridinolyses of eleven \( R_1R_2P(=L)Cl \)-type in MeCN. The arrangement of the substrates in the column for \( P=O \) (1O-7O) and \( P=S \) (1S-6S) systems follows the sequence of the degree of steric hindrance (i.e., bulkiness) of the two ligands.

The \( P=O \) systems are more reactive than their \( P=S \) counterparts for several reasons, the so-called ‘thio effect’ which is mainly the electronegativity difference between O and S that favors O over S. The NBO charges on the P atom of \( P=O \) systems are greater \( (ca. 0.5 - 0.6) \) than those of their \( P=S \) counterparts, implying the electronegativity difference between O and S. Herein, the pyridinolysis rate ratios of \( P=O \) and their \( P=S \) counterparts of \( R_1R_2P(=O)Cl \) type in MeCN at 35.0 °C are great as follows: \( k_2(1O)/k_2(1S) = 137,000; k_2(3O)/k_2(3S) = 42; k_2(4O)/k_2(4S) = 44.6; k_2(5O)/k_2(5S) = 30 \). The correlation \( \Sigma n_I \) with the NBO charge on the P atom reaction center is roughly linear. The plots of the NBO charge on P against \( \Sigma n_I \) yield the slopes of 0.622 (\( r = 0.946 \)) and 0.846 (\( r = 0.918 \)) for \( P=O \) and \( P=S \) systems, respectively. The sequence of the second-order

<table>
<thead>
<tr>
<th>( k_2 (\times 10^2 \text{M}^{-1} \text{s}^{-1}) )</th>
<th>( \text{X} )</th>
<th>( 4-\text{MeO} )</th>
<th>( 4-\text{Me} )</th>
<th>( 3-\text{Me} )</th>
<th>( \text{H} )</th>
<th>( 3-\text{Ph} )</th>
<th>( 3-\text{MeO} )</th>
<th>( 3-\text{Cl} )</th>
<th>( 3-\text{Ac} )</th>
<th>( 4-\text{Ac} )</th>
<th>( 3-\text{CN} )</th>
<th>( 4-\text{CN} )</th>
</tr>
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<tbody>
<tr>
<td>( k_2 \times 10^2 )</td>
<td>96.1 ± 2.3</td>
<td>49.9 ± 1.4</td>
<td>27.1 ± 0.3</td>
<td>18.8 ± 0.4</td>
<td>11.0 ± 0.3</td>
<td>8.29 ± 0.05</td>
<td>2.00 ± 0.04</td>
<td>1.94 ± 0.05</td>
<td>1.27 ± 0.02</td>
<td>0.500 ± 0.012</td>
<td>0.498 ± 0.019</td>
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</table>
rate constants of the pyridinolyses for both the P=O and P=S systems does not show systematic consistency with $\sum_\sigma_i$, NBO charge on P, or even $\sum E_\beta$. These results indicate that the pyridinolysis rates of R$_1$R$_2$P(=L)Cl in MeCN are not dependent upon one dominant factor but on many factors.

The pyridinolyses of 1O, 1S, 3S, 4S, and 5S yield biphasic concave upward free energy correlation (Hammett and Brönsted plots) for substituent X variations with greater and smaller magnitudes of slopes for weakly and strongly basic nucleophiles, respectively. The authors proposed a concerted mechanism with a dominant backside nucleophilic attack towards the Cl leaving group (TSh) for weakly basic pyridines, and a concerted mechanism with a dominant frontside nucleophilic attack (TSf) for strongly basic pyridines, in which the pyridine and Cl occupy adjacent spaces in the TS, on the basis of the concave upward Brönsted plots with smaller $\beta_X$ values for weakly basic pyridines and greater values for strongly basic pyridines.

The greater $\beta_X$ value for the more basic pyridines suggests a dominant frontside attack with greater bond formation compared to a dominant backside attack for the less basic pyridines. It is well known that a weakly basic group has a greater apicophilic site such that an apical approach is favored for such nucleophiles. Since apical bonds are longer than equatorial bonds, a dominant nucleophilic attack should lead to a looser P-N bond in the TBP-5C TS structure and hence a smaller magnitude of $\beta_X$ is obtained, while the equatorial attack should lead to tighter P-N bond in the TBP-5C TS, resulting in a larger magnitude of $\beta_X$. Biphasic concave upward Hammett and Brönsted plots for substituent X variations in the nucleophiles of the reactions of Y-aryl phenyl isothiocyanophosphate with X-pyridines in MeCN was also interpreted as a change in the nucleophile attacking direction from dominant backside for less basic pyridines ($\beta_X = 0.12 - 0.15$) to dominant frontside for more basic pyridines ($\beta_X = 1.13 - 1.28$). It is the suggestion of the authors that the concave upward Hammett and Brönsted plots can also be diagnostic of a change in the attacking direction of the nucleophile depending on the substituents from backside to frontside.

The S$_\alpha$2 reaction mechanisms were proposed for the pyridinolyses of both 7O and 6S on the basis of the negative sign of the CIC$_\alpha$ interactions. A relatively small degree of bond formation in the early TS could be proposed for 7O on the basis of the small magnitudes of $\rho_{XY}$ and $\beta_X$ while a relatively large degree of bond formation in the TS could be proposed for 6S on the basis of the large magnitudes of $\rho_{XY}$ and $\beta_X$.

In the pyridinolysis of 3O ($\beta_X = 0.63$), 4O ($\beta_X = 0.73$), and 5O ($\beta_X = 0.68$), the authors proposed a concerted mechanism with both frontside and backside attacks, 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 $\beta_X$ values. Taking into account $\beta_X = 0.17$ of 1O for weakly basic pyridines where the reaction proceeds through frontside nucleophilic attack, the authors propose a concerted mechanism with greater fraction of a frontside attack than that of a backside attack for the pyridinolysis of 2O with $\beta_X = 0.445$. Both front and backside nucleophilic attack were observed in the anilinolyses of some R$_1$R$_2$P(=L)Cl-type in MeCN.

As seen in Table 3, predominant factor to determine the anilinolysis rates of R$_1$R$_2$P(=L)Cl in MeCN is the degree of steric hindrance, since the anilinolysis rates are inversely proportional to the size of the two ligands ($\sum E_\beta$). The steric effects of the two ligands (R$_1$ and R$_2$) on the anilinolysis rates of P=O...
The pyridinolyses of \( \text{R}_1\text{R}_2\text{P}(=\text{O} \text{ or } \text{S})\text{Cl} \)-type substrates in MeCN (eq 1) are reviewed to obtain systematic information on phosphoryl transfer reaction mechanism.

Pyridinolysis rates of \( \text{R}_1\text{R}_2\text{P}(=\text{O} \text{ or } \text{S})\text{Cl} \)-type substrates in MeCN (eq 1) are reviewed to obtain systematic information on phosphoryl transfer reaction mechanism. The pyridinolysis rates of \( \text{R}_1\text{R}_2\text{P}(=\text{O} \text{ or } \text{S})\text{Cl} \)-type substrates are much greater than those of P=S systems: \( k_{\text{obs}} \) (1O with two small Me)/\( k_{\text{obs}} \) (5O with two large Ph) = 4,520 for P=O, while \( k_{\text{obs}} \) (1S with two small Me)/\( k_{\text{obs}} \) (5S with two large Ph) = 16 for P=S system in MeCN at 55.0 °C. The approach of the aniline nucleophile to the reaction center P should cause extensive steric hindrance when the attacking and leaving groups occupy apical positions in a TBP-5C TS of a backside attack, because of not only a relatively large size of the aniline nucleophile, but also the orientation restriction of the attacking aniline. The lone pair of the amino nitrogen is sp\(^2\)-type, thus the angle of C(α-carbon of phenyl ring)-N (amino nitrogen)-P (reaction center of substrate) would be > 109.5° in the TS. The degree of steric hindrance would thus be greater as the ligands of \( \text{R}_1 \) and \( \text{R}_2 \) become bulkier in the TS. In contrast, the pyridine ring, located more or less parallel to the attacking axis in the TBP-5C TS, would experience much less steric congestion compared to the phenyl ring of the aniline.

The pyridinolysis rate is usually rather faster than the anilinolysis rate for both P=O and P=S systems (except for 1S),\(^{10} \) even taking into account the greater basicity of pyridine than aniline [\( pK_a \) (aniline)] = 10.56 and \( pK_a \) (pyridine)] = 12.33 in MeCN;\(^{11} \) \( pK_a \) (aniline)] = 4.60;\(^{13} \) \( pK_a \) (pyridine)] = 5.17 in water at 25.0 °C]. The rate ratio of \( k_{\text{obs}} \) (35.0 °C)/\( k_{\text{obs}} \) (55.0 °C) increases as the size of the two ligands increases for both P=O and P=S system. However, the rate ratios for P=O are much greater than those for P=S systems.

In summary, the pyridinolysis of diethyl phosphinic chloride (2O) is investigated kinetically in acetonitrile at 45.0 °C. The authors propose a concerted mechanism with greater fraction of a frontside attack than that of a backside attack for the pyridinolysis of 2O. The pyridinolyses of eleven \( \text{R}_1\text{R}_2\text{P}=\text{O} \text{ or } \text{S}\text{Cl} \)-type substrates in MeCN (eq 1) are reviewed to obtain systematic information on phosphoryl transfer reaction mechanism. The pyridinolysis rates of \( \text{R}_1\text{R}_2\text{P}=\text{O} \text{ or } \text{S}\text{Cl} \)-type substrates are not dependent upon one dominant factor but on many factors, while the anilinolysis rates of \( \text{R}_1\text{R}_2\text{P}=\text{O} \text{ or } \text{S}\text{Cl} \)-type substrates are predominantly dependent upon the steric effects of two ligands, \( \text{R}_1 \) and \( \text{R}_2 \).

### Experimental Section

**Materials.** GR grade diethyl phosphinic chloride (2O) (min 97%) was used without further purification. GR grade pyridines were used without further purification. HPLC grade acetonitrile (less than 0.005% water content) was used without further purification.

**Kinetic Procedure.** Conductometric rate measurements were carried out using self-made computer-aided automatic A/D converter conductivity bridges. The pseudo-first-order rate constants (\( k_{\text{obs}} \)) were determined as previously described\(^{14} \) using large excesses of nucleophiles, [2O] = 0.001 M and [\( \text{XC}_2\text{H}_4\text{LN} \)] = 0.01 - 0.08 M. Each pseudo-first-order rate constants value (\( k_{\text{obs}} \)) was averaged obtained from more than three runs, which were reproducible within ±3%.

**Product Analysis.** Diethyl phosphinic chloride was reacted with excess pyridine for more than 15 half-lives at 45.0 °C in acetonitrile. The insoluble products were washed several times with diethyl ether and isolated. The solvent was removed under reduced pressure. Analytical data of the products gave the following results:

\[
\begin{align*}
\text{C}_2\text{H}_5\text{P}=\text{O} & \quad \text{C}_6\text{H}_5\text{N}\text{Cl}\text{H}_2\text{Cl} \\
\text{N} & \quad \text{H} \quad \text{N} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

White gummy liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 1.10, 1.12, 1.14, 1.15, 1.17, 1.19 \) (6H, m, CH\(_3\)), 1.72, 1.74, 1.75, 1.77 (4H, m, CH\(_2\)), 7.26, 7.98, 8.00, 8.01, 8.02, 8.47, 8.91, 8.92, 8.93 (5H, m, pyridine); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta 1.10, 1.12, 1.14, 1.15, 1.17, 1.19 \) (6H, m, CH\(_3\)), 1.72, 1.74, 1.75, 1.77 (4H, m, CH\(_2\)), 20.41, 21.34 (CH\(_2\)), 71.27, 71.28, 127.11, 141.18, 145.57, 149.45 (C=C, pyridine); \(^3\)P NMR (162 MHz, CDCl\(_3\)) \( \delta 67.75 (1P, s, \text{P}=\text{O}); m/z, 217 (M\(^+\)) \).

### References and Notes


8. The P=S systems show more significant substituent effects of the nucleophiles compared to the P=O systems.


10. Note that the reaction temperatures of pyridinolysis (C₅H₅N) and anilinolysis (C₆H₅NH₂) are 35.0 and 55.0 °C, respectively, and that the substituent effects of the nucleophiles are not considered.
