Kinetics and Mechanism of the Aminolysis of Diphenyl Phosphinic Chloride with Anilines

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The aminolyses of diphenyl phosphinic chloride (1) with substituted anilines in acetonitrile at 55.0 °C are investigated kinetically. Large Hammett $\rho_X$ ($\rho_{nuc} = -4.78$) and Brönsted $\beta_X$ ($\beta_{nuc} = 1.69$) values suggest extensive bond formation in the transition state. The primary normal kinetic isotope effects ($k_H/k_D = 1.42-1.82$) involving deuterated aniline (XC\(_6\)H\(_4\)ND\(_2\)) nucleophiles indicate that hydrogen bonding results in partial deprotonation of the aniline nucleophile in the rate-limiting step. The faster rate of diphenyl phosphinic chloride (1) than diphenyl chlorophosphate (2) is rationalized by the large proportion of a frontside attack in the reaction of 1. These results are consistent with a concerted mechanism involving a partial frontside nucleophilic attack through a hydrogen-bonded, four-center type transition state.

Key Words: Aminolysis of diphenyl phosphinic chloride, Frontside nucleophilic attack, Deuterium kinetic isotope effect

Introduction

Nucleophilic substitution at a phosphoryl (P=O) or thio-phosphoryl (P=S) center generally proceeds either through stepwise mechanism with a trigonal bipyramidal pentacoordinate (TBP-5C) intermediate (upper route) or an S\(_N\)\(_2\) mechanism with transition state (TS) (lower route), where the attacking and leaving groups occupy apical positions, i.e., backside nucleophilic attack toward the leaving group.\(^1\)

Stereochemical studies of the displacement of exocyclic groups at phosphorus from a variety of dioxaphosphorinane derivatives show that front- or back-side nucleophilic attack leads to retention or inversion of configuration depending on the nature of the nucleophile, leaving group, solvent, other ionic species present, and other heteroatoms in the six-membered ring.\(^2\)

In previous work, we studied several phosphoryl and thio-phosphoryl transfer reactions kinetically and theoretically.\(^3\) The concerted mechanism with a frontside nucleophilic attack was proposed based on the $\rho_X$, $\beta_X$, $\beta_{nuc}$ and the especially large negative $\rho_{XZ} (= -1.98)$ value for more basic phenolate groups (Z = 4-Cl, 3-Cl, and 3-CN) and less basic pyridines (X = 3-Cl, 3-CH\(_3\)CO, 4-CH\(_3\)CO, 3-CN, and 4-CN) in the reactions of Z-aryl bis(4-methoxyphenyl) phosphates, (4-MeO\(_2\)C\(_6\)H\(_4\)O\(_2\))\(_2\)P(=O)OC\(_6\)H\(_4\)Z, with pyridines, XC\(_6\)H\(_4\)N, in acetonitrile.\(^3d\) The biphasic Hammett (log $k_2$ vs. $\sigma_X$) and Brönsted [log $k_2$ vs. $pK_a(X)$] plots were interpreted as a frontside attack TS for more basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, and 3-C\(_6\)H\(_5\)) and backside attack TS for less basic pyridines (X = 3-CH\(_3\)CO, 3-Cl, 4-CH\(_3\)CO, and 4-CN).\(^3e\) The partial participation of a frontside nucleophilic attack concerted mechanism was proposed for the anilinolysis of aryl phenyl (and 4-chlorophenyl) chlorothiophosphates in acetonitrile.\(^3f\)

To clarify the phosphoryl transfer mechanism, as well as to compare the reactivity of diphenyl chlorophosphate (2)\(^3a\) and diphenyl chlorothiophosphate (3),\(^3f\) here we investigate the aminolysis of diphenyl phosphinic chloride (1) with substituted anilines and deuterated anilines (XC\(_6\)H\(_4\)NH\(_2\) and XC\(_6\)H\(_4\)ND\(_2\)) in acetonitrile at 55.0 °C.

Results and Discussion

The second-order rate constants, $k_H$, for the reactions were obtained as the slope of $k_{\text{obsd}}$ (pseudo-first-order rate constant) against aniline concentration, $[\text{An}]$, $k_{\text{obsd}} = k_0 + k_H[\text{An}] \quad (3)$

where the intercept, $k_0$, was negligible in all cases. No third-order kinetics were observed and no complications were found in the determination of $k_{\text{obsd}}$. The $k_H$ values are summarized in Table 1, together with $k_D$ values involving deuterated anilines (XCH$_4$NCH$_2$D).

The changes in rate observed by varying substituents in the nucleophiles were consistent with the nature of a typical nucleophilic substitution reaction, i.e., the stronger the nucleophile, the faster the rate. Figure 1 shows the nonbonding orbital (NBO) charges and rate ratios of the aminolysis of 1, 2, and 3. The NBO charges of the reaction center P are 1.844 in 1 and 2.230 in 2, which are consistent with the inductive effects of Ph ($\sigma_I = 0.12$) and PhO ($\sigma_I = 0.40$) ligands. Solely considering the positive charge of the reaction center P atom, the aminolysis rate of 2 should be faster than that of 1. However, the observed rate ratio of $k_H(1)/k_H(2) = 1.9$ is opposite to expectation, implying that the reaction rate does not depend only on the positive charge of the reaction center P.

Two phenyl groups are bonded to the reaction center P atom in 1, while an intervening oxygen atom is located between the reaction center P and the phenyl group in 2. As a result, the steric hindrance in 1 would be much larger than that in 2 when the nucleophile attacks opposite the Cl leaving group, i.e., backside nucleophilic attack. This result strongly suggests that the reaction of 1 with anilines does not simply proceed by a backside nucleophilic attack. The slower rate of 3 (P=S system) than those of 1 and 2 (P=O system) is attributed to several causes, the so-called “thio effect”, which is mainly the electronegativity difference between O and S. 1c,6

The $pK_a(X)$ values in H$_2$O are used to obtain the Brønsted $\beta_X$ value as shown in Figure 2. The $\Delta pK_a = pK_a(\text{MeCN}) - pK_a(\text{H}_2\text{O})$ values for structurally similar amines are nearly constant, so determination of $\beta_X$ by plotting $\log k_H(\text{MeCN})$ against $pK_a(\text{H}_2\text{O})$ is probably justified. 7 The magnitudes of Hammett $\rho_X (-4.78)$ and Brønsted $\beta_X (1.69)$ values are both large, suggesting extensive bond formation in the TS. The obtained $\beta_X$ value is considerably larger than those of other phosphoryl and thiophosphoryl reactions in which the reactions proceed through a concerted mechanism. The $\beta_X$ values of the reactions of (i) 4-nitrophenyl dimethyl phosphiniothioate with phenoxides, 1c (ii) 4-nitrophenyl diphenyl phosphate with phenoxides, 8 (iii) 4-nitrophenyl diphenyl phosphinate with phenoxides.

![Figure 1](image-url)  

Figure 1. The B3LYP/6-311+G(d,p) geometries and nonbonding orbital (NBO) charges of 1, 2, 3. The relative rate ratios are for unsubstituted aniline (C$_6$H$_5$NH$_2$).

<table>
<thead>
<tr>
<th>X</th>
<th>$k_H$ ($\times 10^4$/M$^{-1}$s$^{-1}$)</th>
<th>$k_D$ ($\times 10^4$/M$^{-1}$s$^{-1}$)</th>
<th>$k_H/k_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-CH$_3$O</td>
<td>524 ± 14</td>
<td>288 ± 7.9</td>
<td>1.82 ± 0.070</td>
</tr>
<tr>
<td>4-CH$_3$</td>
<td>156 ± 3.2</td>
<td>86.3 ± 1.4</td>
<td>1.81 ± 0.047</td>
</tr>
<tr>
<td>3-CH$_3$</td>
<td>33.7 ± 1.0</td>
<td>18.7 ± 0.56</td>
<td>1.80 ± 0.076</td>
</tr>
<tr>
<td>H</td>
<td>17.3 ± 0.54</td>
<td>9.69 ± 0.33</td>
<td>1.79 ± 0.082</td>
</tr>
<tr>
<td>3-CH$_3$O</td>
<td>3.13 ± 0.12</td>
<td>2.20 ± 0.11</td>
<td>1.42 ± 0.090</td>
</tr>
<tr>
<td>4-Cl</td>
<td>1.87 ± 0.077</td>
<td>1.32 ± 0.041</td>
<td>1.42 ± 0.073</td>
</tr>
<tr>
<td>3-Cl</td>
<td>0.476 ± 0.018</td>
<td>0.335 ± 0.012</td>
<td>1.42 ± 0.074</td>
</tr>
</tbody>
</table>

*Correlation coefficients (r) were better than 0.997. *r ≥ 0.997. *Standard deviation.

Table 1. Second-Order Rate Constants, $k_H$ and $k_D$ ($\times 10^4$/M$^{-1}$s$^{-1}$), of the Aminolysis of Diphenyl Phosphinic Chloride (1) with XCH$_2$NH$_2$ and XCH$_2$NHD$_2$ in Acetonitrile at 55.0 °C
The especially large secondary inverse kinetic isotope effects (KIEs; $\rho_X$) in the anilinolysis of $\text{XC}_6\text{H}_4\text{ND}_2$ are assumed for the anilinolysis of $\text{XC}_6\text{H}_4\text{NH}_2$ to be the same as the $\rho_X$ values of $\text{XC}_6\text{H}_4\text{NH}_2$ in water.

When the frontside nucleophilic attack is major direction, greater deprotonation would occur with a greater bond order $\beta_X$. As a result, the real primary KIE due to the hydrogen bond becomes larger than the obtained KIEs, which is suggested for the anilinolysis of 2 and 3 and the product-like TS in the anilinolysis of 1 based on several reasons, mainly the primary KIEs, $k_\text{H}/k_\text{D} = 1.1-1.3$. This KIEs with deuterated anilines are summarized in Table 2 (see also Table 2). As observed in the anilinolysis of 3, the $k_\text{H}/k_\text{D}$ values of 1 are all greater than unity, $k_\text{H}/k_\text{D} = 1.4-1.8$, indicating that partial deprotonation of the aniline nucleophile occurs in the rate-limiting step by hydrogen bonding.

Two possible TS structures can be proposed: hydrogen bonding between the Cl leaving group and the hydrogen of the N-H(D) moiety (4) or between the polar oxygen in P=O and the hydrogen of the N-H(D) moiety in aniline (5).

Buncel$^{12}$ and Um$^{13}$ reported a four-membered TS (6) in the ethanalysis of the phosphinates, paraxon and parathion, caused by alkali metal ions. In such a manner, the catalytic effect increases with increasing positive charge density of M$^\text{+}$ ions. The catalytic effect of the M$^\text{+}$ ions is stronger in a P=O than in a P=S system, due to the polarizable S atom. Positive charge development on the hydrogen of the N-H moiety in the TS would be much smaller than that of M$^\text{+}$ ions, so hydrogen bonding involving the strong acceptor P=O, TS 5, is not feasible in the present work. Moreover, the secondary inverse KIE, $k_\text{H}/k_\text{D} < 1$, of the anilinolysis of 2 and primary normal KIE, $k_\text{H}/k_\text{D} > 1$, of the anilinolysis of 3 cannot be rationalized by TS 5. Therefore, the possibility of TS 5 can be neglected in the present work.

When the aniline nucleophile attacks backside toward the Cl leaving group, the steric effect on the TS would be larger in 1 than in 3 due to the intervening oxygen atom between the reaction center P atom and phenyl group in 3 (see Figure 1). As a result, the proportion of frontside nucleophilic attack (TS 4) would be greater in 1 than in 3; therefore, the $k_\text{H}/k_\text{D}$ values of 1 (1.42-1.82) are larger than those of 3 (1.11-1.27). The faster rate of 1 than 2 could be rationalized by the large proportion of frontside attack in the reaction of 1, where steric hindrance does not play an important role.

The obtained KIEs would be the sum of the primary KIE, $k_\text{H}/k_\text{D} > 1$, due to partial deprotonation as shown in TS 4, and the secondary inverse KIE, $k_\text{H}/k_\text{D} < 1$, due to steric hindrance that increases the out-of-plane bending vibrational frequencies of N-H(D) bonds in the TS for a backside attack. As a result, the real primary KIE due to the hydrogen bond between the hydrogen of N-H(D) moiety and the Cl leaving group should be greater than the observed value.

When the frontside nucleophilic attack is major direction, greater deprotonation would occur with a greater bond formation, i.e., the stronger nucleophile ($\partial\sigma_X < 0$) leads to a...
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greater hydrogen bond formation. Then the observed primary KIE, \( k_d/k_0 \), values greater than unity, may be proportional to the degree of hydrogen bond formation and the expected sequence of the \( k_d/k_0 \) values is \( X = 4\text{-MeO} > 4\text{-Me} > 3\text{-Me} > H > 3\text{-MeO} > 4\text{-Cl} > 3\text{-Cl}, \) similar to the observed sequence, \( X = 4\text{-MeO} \geq 4\text{-Me} \geq 3\text{-Me} \geq H > 3\text{-MeO} > 4\text{-Cl} = 3\text{-Cl}. \) The observed sequence of the \( k_d/k_0 \) values in Table 2 shows the same tendency as in 1, \( X = 4\text{-MeO} > H > 4\text{-Cl} \) (footnote of Table 2). When the backside nucleophilic attack is major direction, which leads to the secondary inverse KIEs, \( k_d/k_0 < 1 \), the observed sequence of the \( k_d/k_0 \) values in Table 2 shows the same tendency as in 1, \( X = 4\text{-MeO} > H > 4\text{-Cl} \) (footnote of Table 2), and obtained substituent effects of \( X \) on the KIEs may be explained by the larger magnitudes of \( \rho_X \) and \( \beta_X \) values of \( S < 1 \) and \( S > 3 \), respectively). When the front and back side attack is comparable, the substituent effects of \( X \) on the KIEs would be complicated. The discrepancy between the expected and obtained substituent effects of \( X \) on the KIEs may be due to the proportion of frontside and backside nucleophilic attack, \( k_d/k_0 \) values in smaller \( k_d/k_0 \) value and more backside attack results in smaller \( k_d/k_0 \) value and more backside attack results in smaller \( k_d/k_0 \) value.

The larger magnitudes of \( \rho_X \) and \( \beta_X \) values of 1 (–4.78 and 1.69) respectively) compared to 2 (–3.74 and 1.35, respectively) and 3 (–3.88 and 1.36, respectively) suggest that 1 has a larger, more product-like TS than 2 and 3. The magnitudes of \( \rho_X \) and \( \beta_X \) values of 1 (–4.56 and 1.62, respectively) with deuterated anilines \((XC_6H_4ND_2)\) are somewhat smaller than those with anilines \((XC_6H_4NH_2)\), suggesting less sensitivity to substituent effect of deuterated anilines than of anilines.

Summary

The reactions of diphenyl phosphinic chloride (1) with X-anilines were studied kinetically in acetonitrile at 55.0 °C. When substituents in the nucleophiles were varied, the rate changes were consistent with the nature of a typical nucleophilic substitution reaction. Structure-reactivity relationship between 1, 2, and 3 was discussed based on NBO charges and steric effects. The primary normal KIEs \((k_d/k_0 = 1.42-1.82)\) involving deuterated aniline \((XC_6H_4ND_2)\) nucleophiles were obtained and were consistent with a partial frontside attack concerted mechanism through a hydrogen-bonded four-center type TS. The large magnitudes of \( \rho_X \) and \( \beta_X \) values of 1 (–4.78 and 1.69) suggest a late, product-like TS.

Experimental Section

Materials. Diphenyl phosphinic chloride, 98% (substrate), and HPLC grade acetonitrile (water content is less than 0.0005%) were used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described. Deuterated anilines were prepared by heating anilines with D_{2}O at 85 °C for 72 h and, after numerous attempts, were more than 98% deuterated, as confirmed by 1H-NMR.

Kinetics Measurement. Rates were measured conductometrically as described previously. For the present work, [substrate] = 1 × 10^{-3} M and [An] = 0.03-0.15 M were used. We tried at least five concentrations of anilines. Pseudo-first-order rate constant values were the average of three runs, which were reproducible within ± 3%.

Product Analysis. Diphenyl phosphinic chloride was refluxed with excess anilines \((XC_6H_4NH_2; X = 4\text{-CH}_3O, H, \) for more than 15 half-lives at 55.0 °C in acetonitrile, as described. Analytical data of the products gave the following results:

\[
(C_6H_5)_2P(=O)(NH-C_6H_4-4-CH_2O). \quad \text{Purple Solid; mp 142-144 °C; IR (nujol mull) 3375 (NH), 3124 (C-H, aromatic); 1H NMR (400 MHz, DMSO-d_6) }\delta = 3.67 (3H, s, CH_3O), 6.88 (2H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.48-7.54 (6H, m, benzene), 7.76-7.81 (4H, m, benzene), 8.00 (1H, d, J = 11.6 Hz, NH); \text{IR (nujol mull) 3375 (NH), 3124 (C-H, aromatic); 13C NMR (100 MHz, DMSO-d_6) }\delta = 142-144 °C; \text{IR (nujol mull) 3179 (NH), 3089 (C-H, aromatic), 2724 (CH_3), 1511, 1378 (P-C_6H_5), 1463 (CH_3-O).}
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References

