Kinetics and Mechanism of the Anilinolysis of O-Ethyl Phenyl Phosphonochloridothioate 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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The nucleophilic substitution reactions of O-ethyl phenyl phosphonochloridothioate with substituted anilines (XNC6H4NH2) and deuterated anilines (XNC6H4ND2) are kinetically investigated in acetonitrile at 55.0 °C. The deuterium kinetic isotope effects (DKIEs) invariably increase from a secondary inverse DKIE (kD/kH = 0.93) to a primary normal DKIE (kD/kH = 1.28) as the substituent of nucleophile (X) changes from electron-donating to electron-withdrawing. These can be rationalized by the gradual transition state (TS) variation from a backside to frontside attack. A concerted S2 mechanism is proposed. A trigonal bipyramidal TS is proposed for a backside attack while a hydrogen-bonded, four-center-type TS is proposed for a frontside attack.

Key Words : Phosphoryl transfer reaction, Anilinolysis, O-Ethyl phenyl phosphonochloridothioate, Deuterium kinetic isotope effect

Introduction

In previous work, this lab reported upon various types of phosphoryl and thiophosphoryl transfer reactions, experimentally and theoretically. The kinetics and mechanism of the anilinolyses of (Lig1)(Lig2)P(=O or =S)Cl-type substrates in acetonitrile (MeCN) were investigated by means of the deuterium kinetic isotope effects (DKIEs) involving deuterated anilines (XNC6H4ND2), selectivity parameters, and steric effects of the two ligands (Lig1 and Lig2).

It is well known that the DKIEs are one of the strong tools to clarify the reaction mechanism. The DKIEs can be only secondary inverse (kD/kH < 1) in a normal S2 reaction, since the N–H(D) vibrational frequencies invariably increase upon going to the transition state (TS) (in-line-type TSb in Scheme 1; backside nucleophilic attack), given the increase in steric hindrance in the bond formation step; the greater the bond formation, the greater the steric congestion occurs, and the smaller the kD/kH value becomes.1 In contrast, when partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding (hydrogen-bonded, four-center-type TSf in Scheme 1; frontside nucleophilic attack), the DKIEs are primary normal (kD/kH > 1); the greater the extent of the hydrogen bond that occurs, the greater the kD/kH value becomes.2 The real primary normal DKIE due to the hydrogen bond between the hydrogen of the N–H(D) moiety and Cl leaving group should be greater than the observed value since the observed DKIEs would be the sum of: (i) the primary normal DKIE, kD/kH > 1, because of the partial deprotonation of one of the two N–H(D) bonds in the TSf for a frontside attack; (ii) the secondary inverse DKIE, kD/kH < 1, because of the steric hindrance that increases the out-of-plane bending vibrational frequencies of the other N–H(D) bond in TSf for a frontside attack; (iii) lowering the kD/kH value because of the nonlinear and unsymmetrical structure of N−H(D)−Cl in TSf; and finally (iv) lowering the kD/kH value because of heavy atom (N in the nucleophile and Cl in the leaving group) contribution to the reaction-coordinate motion. When the reaction proceeds simultaneously through both pathways, backside (TSb) and frontside (TSf) attack, the observed DKIEs are the sum of both effects, secondary inverse and primary normal, and the obtained value of kD/kH can be greater or lesser than unity depending on the proportion of the two pathways.

The anilinolyses of phosphonochloridothioates showed surprising results of DKIEs in MeCN:1 (i) In Y-O-aryl methyl phosphonochloridothioates [1: Me(YC6H4O)P(=S)Cl],3,4 nonlinear free-energy correlations, biphasic concave downward Hammett and Brønsted plots with a break region between X = H and 4-Cl, were observed. The DKIEs are distinctly divided into two parts, unprecedented great secondary inverse (kD/kH = 0.37-0.57 << 1) with less basic anilines (X = 4-Cl, 3-Cl, 3-NO2) and primary normal (kD/kH = 1.03-1.30) with more basic anilines (X = 4-MeO, 4-Me, H), rationalized by backside attack TSb with less basic anilines while frontside attack TSf with more basic anilines. The extraordinary secondary inverse DKIEs with less basic anilines suggest that the steric congestion in the TS is huge and the degree of bond formation is really extensive; (ii) In Y-O-aryl phenyl phosphonochloridothioates [3: Ph(YC6H4O)P(=S)Cl],5,6 the DKIEs invariably increase from

Scheme 1. Backside attack TSb and frontside attack involving hydrogen-bonded, four-center-type TSf (L = H or D; A = O or S; Lig1 and Lig2 represent the two ligands).
The nucleophilic substitution reactions of O-ethyl phenyl phosphonochloridothioate (2) with \( \text{XC}_6\text{H}_5\text{NH}_2\text{Cl}_2 \) in MeCN at 55.0 °C.

The second-order rate constants \( (k_{0}/k_{0}) \) were determined at least five concentrations of anilines. The linear plots of Eq. (1) suggest that there is no base-catalysis or noticeable side reaction and that the overall reaction is described by Scheme 2.

\[
k_{\text{obsd}} = k_0 + k_{10[D]} [\text{XC}_6\text{H}_5\text{NH}_2(D_2)]
\]

The second-order rate constants \( (k_0 \text{ and } k_{10}) \) are summarized in Table 1, together with the deuterium kinetic isotope effects (DKIEs; \( k_0/k_{10} \)) and Hammett \( \rho_X \) and Brønsted \( \beta_X \) selectivity parameters. The \( pK_a(X) \) values of the X-anilines in water were used to obtain the Brønsted \( \beta_X \) values in MeCN, and this procedure was justified experimentally and theoretically.\(^5\) The values of \( pK_a(X) \) and \( \sigma_X \) of the deuterated X-anilines are assumed to be identical to those of the X-anilines. Perrin and coworkers reported that the basicities of \( \beta \)-deuterated analogs of benzylamine, \( N,N \)-dimethylaniline and methylamine increase roughly by 0.02 pK\(_a\) units per deuterium, and that these effects are additive.\(^6\) Thus, the

\[
\rho = \frac{\rho_X}{\beta_X}
\]

The observed pseudo-first-order rate constants \( (k_{\text{obsd}}) \) were found to follow Eq. (1) for all the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The \( k_0 \) values were negligible \( (k_0 \approx 0) \) in MeCN. The

\[
k_0 = k_{10[D]}[\text{XC}_6\text{H}_5\text{NH}_2(D_2)]
\]

The B3LYP/6-311+G(d,p) geometry, bond angles, and natural bond order (NBO) charges of the two ligands.

![Figure 1](image1.png)

Figure 1. The B3LYP/6-311+G(d,p) geometry of O-ethyl phenyl phosphonochloridothioate (2) in the gas phase.

![Figure 2](image2.png)

Figure 2. The Hammett plots (log \( k_{10[D]} \) vs \( \sigma_X \)) of the reactions of O-ethyl phenyl phosphonochloridothioate (2) with \( \text{XC}_6\text{H}_5\text{NH}_2(D_2) \) in MeCN at 55.0 °C.

Table 1. The Second-Order Rate Constants \( (k_{10[D]} \times 10^6/M^2 s^{-1}) \), Selectivity Parameters \( (\rho_X \text{ and } \beta_X) \), and DKIEs \( (k_0/k_{10}) \) of the Reactions of O-Ethyl Pheny]l Phosphonochloridothioate (2) with \( \text{XC}_6\text{H}_5\text{NH}_2(D_2) \) in MeCN at 55.0 °C.

<table>
<thead>
<tr>
<th>( \text{X} )</th>
<th>( k_{10} \times 10^6 )</th>
<th>( k_0 \times 10^6 )</th>
<th>( k_0/k_{10} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeO</td>
<td>61.5 ± 0.1 ( ^\circ )</td>
<td>66.1 ± 0.3</td>
<td>0.930 ± 0.005 ( ^\circ )</td>
</tr>
<tr>
<td>4-Me</td>
<td>28.3 ± 0.1</td>
<td>28.8 ± 0.1</td>
<td>0.983 ± 0.005</td>
</tr>
<tr>
<td>3-Me</td>
<td>10.9 ± 0.1</td>
<td>10.4 ± 0.1</td>
<td>1.05 ± 0.01</td>
</tr>
<tr>
<td>H</td>
<td>6.93 ± 0.01</td>
<td>5.93 ± 0.01</td>
<td>1.17 ± 0.01</td>
</tr>
<tr>
<td>4-MeO</td>
<td>2.77 ± 0.01</td>
<td>2.30 ± 0.01</td>
<td>1.20 ± 0.01</td>
</tr>
<tr>
<td>4-CI</td>
<td>1.07 ± 0.01</td>
<td>0.883 ± 0.002</td>
<td>1.21 ± 0.01</td>
</tr>
<tr>
<td>3-CI</td>
<td>0.370 ± 0.001</td>
<td>0.290 ± 0.001</td>
<td>1.28 ± 0.01</td>
</tr>
<tr>
<td>( \sigma_X )</td>
<td>3.47 ± 0.03</td>
<td>3.69 ± 0.03</td>
<td>1.05</td>
</tr>
<tr>
<td>( \beta_X )</td>
<td>1.23 ± 0.04 ( ^\circ )</td>
<td>1.31 ± 0.05 ( ^\circ )</td>
<td>1.05</td>
</tr>
</tbody>
</table>

\( ^\circ \)The values were taken from ref. 7. The \( pK_a(X) \) values of X-anilines in water were taken from ref. 8. \( ^\circ \)Standard deviation. \( ^\circ \)Correlation coefficient. \( r = 0.999, \text{r}^\circ = 0.999, \text{r}^\circ = 0.999, \text{r}^\circ = 0.999. \) Standard error \( \approx 1/ \sqrt{(k_0/(\Delta k_0)^2 + (k_0/k_{10})^2) \times (\Delta k_0)^2} \) from ref. 9.
Anilinolyses of O-Ethyl Phenyl Phosphonochloridothioate


pK_a(X) values of deuterated X-anilines may be slightly greater than those of X-anilines, however, the difference is too small to be taken into account. Figures 2 and 3 show the Hammett (log k_{3ED}/vs pK_a(X)) and Brönsted (log k_{3ED}/vs pK_a(X)) plots with X, respectively. The stronger nucleophile leads to the faster rate as observed in a typical nucleophile substitution reaction with positive charge development at the nucleophilic N atom in the TS. The DKIES invariably increase from the secondary inverse (k_{i}/k_{o} = 0.93-0.98 < 1) with X = (4-MeO, 4-Me) to primary normal (k_{i}/k_{o} = 1.05-1.28 > 1) with X = (3-Me, H, 3-MeO, 4-Cl, 3-Cl) as the aniline becomes less basic. The magnitudes of n_δ and β_δ values with anilines are slightly smaller than those with deuterated anilines, suggesting less sensitive to substituent X effect of anilines compared to that of deuterated anilines.

The second-order rate constants (k_{i}) with unsubstituted aniline (C_6H_5NH_2) at 55.0 °C, NBO charges at the reaction center P atom [B3LYP/6-311+G(d,p) level of theory] in the gas phase, Brönsted coefficients (β_{3ED}), cross-interaction constants (CICs, ρ_{XY}), and DKIES (k_{i}/k_{o}) of the reactions of 1-4 with XC_6H_4NH_2(D_2) in MeCN at 55.0 °C are summarized in Table 2. There is no correlation between the anilinolysis rates of 1-3 and positive charges at the reaction center P atom, implying that the inductive effects of the two ligands do not play any role to decide the reactivity of anilinolyses of R_1(R_2O)P(=S)Cl-type substrates. The anilinolysis rates of 1-3 are inversely proportional to the size of the two ligands, 3(Ph,PhO) > 2(Ph,EtO) > 1(Me,PhO), suggesting that the steric effects of the two ligands are the major factor to determine the anilinolysis rates. The larger the two ligands, the steric effects become greater in the TS, and the rate becomes slower. The size of PhS is more or less larger than that of PhO and, thus, the steric effects of the two ligands of 4 with PhS are somewhat greater than those of 3 with PhO in the TS. However, the anilinolysis rate of 4 is nine times slower than that of 3 which cannot be rationalized by the difference of the two ligands. The considerably slower rate of 4 compared to that of 3 may be due to the difference of NBO charge at P atom, (NBO charge) = 1.462(3)-0.999(4) = 0.463.

The cross-interaction constant (CIC; ρ_{XY}) is negative in a normal S_n2 reaction (or in a stepwise reaction with a rate-limiting bond formation) and positive in a stepwise reaction with a rate-limiting leaving group expulsion from the intermediate. The magnitude of the CIC is inversely proportional to the distance between X and Y through the reaction center; the tighter the TS, the greater the magnitude of the CIC. Here, X and Y denote the substituents of the nucleophile and substrate, respectively. A concerted mechanism was proposed with more basic anilines based on negative ρ_{XY} (−0.95) value while a stepwise mechanism with a rate-limiting leaving group departure from the intermediate with less basic anilines based on the positive ρ_{XY} (0.77) value for the anilinolysis of 1. A concerted mechanism was proposed on the basis of negative ρ_{XY} [= −0.38(3) and −0.31(4)] values for the anilinolyses of 3 and 4, respectively.

In the present work, a concerted mechanism is proposed on the basis of: (i) the Brönsted coefficient (β_{3ED} = 1.23: comparable with β_{3ED}(3) = 1.22-1.33 and β_{3ED}(4) = 1.21-1.25); (ii) and the same variation trends of the DKIES with X from secondary inverse to primary normal DKIES as observed in 3, where the magnitude of k_{i}/k_{o} increases with a weaker nucleophile. The DKIES (k_{i}/k_{o} = 0.93-1.28) suggest that the nucleophile attacking direction is changed from predominant backside attack (TSb; Scheme 1) to predominant frontside attack (hydrogen-bonded, four-center-type TSb; Scheme 1) as the aniline becomes less basic. These phenomena were also observed in the anilinolysis of 3. These results suggest that the fraction of backside attack gradually decreases, while that of frontside attack gradually increases as the aniline becomes weaker.

Activation parameters, enthalpy and entropy of activation.

Table 2. Summary of the Second-Order Rate Constants (k_{i} × 10^{7}/M·l·s^{-1}) with C_6H_5NH_2, NBO Charges at the Reaction Center P Atom, Brönsted Coefficients (β_{3ED}), CICs (ρ_{XY}), and DKIES (k_{i}/k_{o}) for the Reactions of 1-4 with XC_6H_4NH_2(D_2) in MeCN at 55.0 °C

<table>
<thead>
<tr>
<th>Substrate</th>
<th>10^{7}k_i</th>
<th>charge at P</th>
<th>β_{3ED}</th>
<th>ρ_{XY}</th>
<th>k_{i}/k_{o}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Me(YC_6H_5O)P(=S)Cl</td>
<td>7.25^a</td>
<td>1.432^a</td>
<td>0.14-0.46</td>
<td>3</td>
<td>1.03-1.30</td>
</tr>
<tr>
<td>2: Ph(EtO)P(=S)Cl</td>
<td>6.93</td>
<td>1.478</td>
<td>1.31-1.54</td>
<td>−0.95, +0.77</td>
<td>0.37-0.57</td>
</tr>
<tr>
<td>3: Ph(YC_6H_5O)P(=S)Cl</td>
<td>1.50^b</td>
<td>1.462^b</td>
<td>1.23</td>
<td>–</td>
<td>0.93-1.28</td>
</tr>
<tr>
<td>4: Ph(YC_6H_5S)P(=S)Cl</td>
<td>0.175^b</td>
<td>0.999^b</td>
<td>1.21-1.25</td>
<td>−0.31</td>
<td>0.65-0.98</td>
</tr>
</tbody>
</table>

^aThe value with unsubstituted aniline. ^bThe value with Y = H. ^X = (4-MeO, 4-Me, H). ^X = (4-Cl, 3-Cl, 3-NO_2).
are determined for the anilinolysis (with C₂H₅NH₂) of 2 in Table 3. The enthalpy of activation is relatively low (4.6 mol⁻¹ K⁻¹) and entropy of activation is relatively large negative values (–55 cal mol⁻¹ K⁻¹). The relatively low of activation enthalpy and large negative value of activation entropy are typical for the aminolyses of P=S systems.

**Experimental Section**

**Materials.** Phenyliophosphonic dichloride (more than 98.0%), ethanol (more than 99.8%) were used for substrate synthesis, and HPLC grade acetonitrile (water content is less than 0.005%) was used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described. Deuteriated anilines were synthesized by heating anilines and deuterium oxide (99.9 atom %D) and one drop of HCl as catalyst at 85 °C for 72 hr, and the product gave the following results (see Supporting Information):

**Product Analysis.** O-Ethyl phenyl phosphonochloridothioate was reacted with excess aniline, for more than 15 half-lives at 55.0 °C in MeCN. The aniline hydrochloride salt was separated by filtration. Acetonitrile was evaporated under reduced pressure. The product was isolated with ether by a work-up process and dried over anhydrous MgSO₄. After filtration the product was isolated by evaporating the solvent under reduced pressure. The analytical and spectroscopic data of the product gave the following results (see Supporting Information):

**Table 3. Activation Parameters for the Reactions of O-Ethyl Phenyl Phosphonochloridothioate (2) with Aniline (C₂H₅NH₂) in MeCN**

<table>
<thead>
<tr>
<th>t°C</th>
<th>kₜ × 10⁻¹⁰M⁻¹s⁻¹</th>
<th>∆Hθ/kcal mol⁻¹</th>
<th>∆Sθ/cal mol⁻¹ K⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.0</td>
<td>5.27 ± 0.01</td>
<td>4.6</td>
<td>55</td>
</tr>
<tr>
<td>55.0</td>
<td>6.93 ± 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.0</td>
<td>8.63 ± 0.03</td>
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**References**


