

Kinetics and Mechanism of the Anilinolysis of Diisopropyl Chlorophosphate in Acetonitrile

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The nucleophilic substitution reactions of diisopropyl chlorophosphate (**3**) with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) are investigated kinetically in acetonitrile at 55.0 °C. The anilinolysis rate of **3** is rather slow to be rationalized by the conventional stereoelectronic effects. The obtained deuterium kinetic isotope effects (DKIEs; $k_{\text{H}}/k_{\text{D}}$) are secondary inverse ($k_{\text{H}}/k_{\text{D}} = 0.71\text{--}0.95$) with maximum magnitude at X = H. A concerted mechanism involving predominant backside nucleophilic attack is proposed on the basis of the secondary inverse DKIEs.

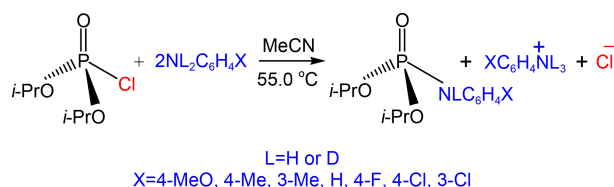
Key Words : Phosphoryl transfer reaction, Anilinolysis, Diisopropyl chlorophosphate, Deuterium kinetic isotope effect

Introduction

Nucleophilic substitution reactions at tetracoordinated phosphorus proceed through trigonal-bipyramidal pentacoordinate (TBP-5C) intermediate or concertedly through a single transition state (TS). The experimental (anilinolysis,¹ pyridinolysis,² and benzylaminolysis³) and theoretical⁴ studies on the phosphoryl and thiophosphoryl transfer reactions have been carried out extensively by this lab. In the present work, the nucleophilic substitution reactions of diisopropyl chlorophosphate (**3**) with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) are investigated kinetically in acetonitrile at 55.0 ± 0.1 °C (Scheme 1). The aim of this work is to gain further information into the phosphoryl transfer reactions, as well as to compare with the reaction mechanism and deuterium kinetic isotope effects (DKIEs; $k_{\text{H}}/k_{\text{D}}$) on the anilinolyses of (R₁O)(R₂O)-P(=O)Cl-type substrates: dimethyl [**1**: (MeO)₂P(=O)Cl],^{1g} diethyl [**2**: (EtO)₂P(=O)Cl],^{1g} ethyl phenyl [**4**: (EtO)(PhO)-P(=O)Cl],^{1f} and diphenyl [**5**: (PhO)₂P(=O)Cl]^{1a} chlorophosphates. The numbering of the substrates of **1–5** follows the sequence of the size of the two ligands, R₁O and R₂O. The reactivities of the substrates are discussed on the basis of the steric effects of the two ligands (R₁O and R₂O). The substituent effects on the DKIEs are discussed on the basis of the variation trends of the magnitudes of the DKIEs.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq. (1) for all of the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The k_0 values were negligible ($k_0 = 0$) in MeCN. The second-order rate constants ($k_{\text{H(D)}}$) were determined for at least five concentrations of anilines. The linear plots of eq. (1) suggest that there are no base-catalysis or noticeable side reactions and that the overall reaction is described by



Scheme 1. The studied reaction system.

Scheme 1.

$$k_{\text{obsd}} = k_0 + k_{\text{H(D)}}[\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)] \quad (1)$$

The k_{H} and k_{D} values are summarized in Table 1, together with the DKIEs ($k_{\text{H}}/k_{\text{D}}$) and the Hammett ρ_{X} and Brønsted β_{X} selectivity parameters. The $\text{p}K_{\text{a}}(\text{X})$ values of the X-anilines in water were used to obtain the Brønsted β_{X} values in MeCN, and this procedure was justified experimentally and theoretically.⁵ The values of $\text{p}K_{\text{a}}(\text{X})$ and σ_{X} of the deuterated X-anilines are assumed to be identical to those of

Table 1. The Second-Order Rate Constants ($k_{\text{H(D)}} \times 10^4/\text{M}^{-1} \text{ s}^{-1}$), Selectivity Parameters (ρ_{X} and β_{X}),^a and DKIEs ($k_{\text{H}}/k_{\text{D}}$) of the Reactions of Diisopropyl Chlorophosphate (**3**) with XC₆H₄NH₂(D₂) in MeCN at 55.0 °C

X	$k_{\text{H}} \times 10^4$	$k_{\text{D}} \times 10^4$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	47.1 ± 0.4 ^b	53.7 ± 0.4	0.877 ± 0.010 ^g
4-Me	22.1 ± 0.2	24.5 ± 0.2	0.902 ± 0.011
3-Me	9.70 ± 0.08	10.5 ± 0.1	0.924 ± 0.012
H	7.10 ± 0.06	7.51 ± 0.07	0.945 ± 0.012
4-F	4.97 ± 0.04	5.70 ± 0.04	0.872 ± 0.009
4-Cl	1.23 ± 0.01	1.60 ± 0.01	0.769 ± 0.008
3-Cl	0.490 ± 0.005	0.691 ± 0.004	0.709 ± 0.008
$-\rho_{\text{X}}$	3.08 ± 0.04 ^c	2.92 ± 0.05 ^e	
β_{X}	1.10 ± 0.04 ^d	1.04 ± 0.05 ^f	

^aThe σ values were taken from ref. 7. The $\text{p}K_{\text{a}}$ values of X-anilines in water were taken from ref. 8. ^bStandard deviation. ^cCorrelation coefficient, $r = 0.999$. ^d $r = 0.998$. ^e $r = 0.998$. ^f $r = 0.997$. ^gStandard error $\{= 1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2 \times (\Delta k_{\text{D}})^2]^{1/2}\}$ from ref. 9.

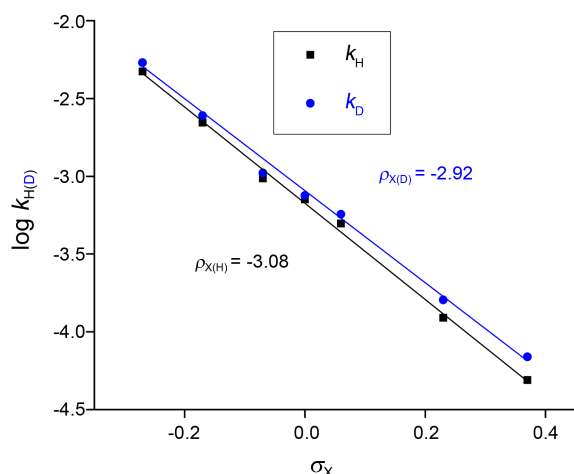


Figure 1. The Hammett plots ($\log k_{H(D)}$ vs σ_X) of the reactions of diisopropyl chlorophosphate (**3**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C.

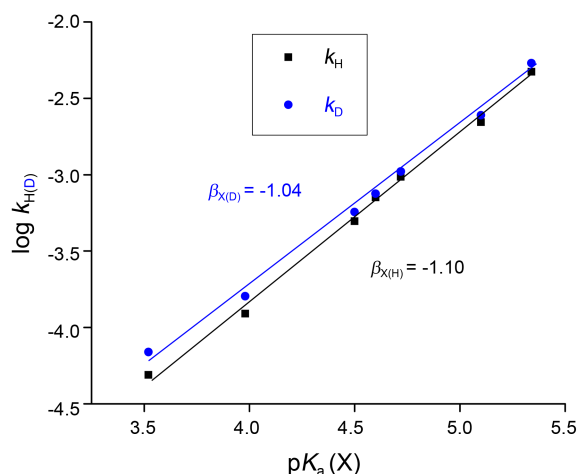


Figure 2. The Brønsted plots [$\log k_{H(D)}$ vs $\text{p}K_a(\text{X})$] of the reactions of diisopropyl chlorophosphate (**3**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C.

the X-anilines. The $\text{p}K_a(\text{X})$ 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.⁶ Figures 1 and 2 show the Hammett ($\log k_{H(D)}$ vs σ_X) and Brønsted [$\log k_{H(D)}$ vs $\text{p}K_a(\text{X})$] plots, respectively, for substituent X variations in the nucleophiles. The stronger nucleophile leads to the faster rate as observed in a typical nucleophilic substitution reaction. The secondary inverse DKIEs ($k_H/k_D < 1$) are observed all of the nucleophiles. However, the values of DKIEs invariably increase as the nucleophile changes from X = 4-MeO ($k_H/k_D = 0.877$) to X = H (max; $k_H/k_D = 0.945$) and then invariably decrease from X = H to X = 3-Cl (min; $k_H/k_D = 0.709$).

The second-order rate constants (k_H) with unsubstituted aniline, summary of NBO charge at the reaction center P atom [B3LYP/6-311+G(d,p)]¹⁰ in the gas phase, summation of the Taft's steric constants of R_1 and R_2 [$\Sigma E_S = E_S(R_1) + E_S(R_2)$],¹¹ Brønsted coefficients ($\beta_{X(H)}$ and $\beta_{X(D)}$), DKIEs (k_H/k_D), and the variation trends of DKIEs depending on the substituent X in the nucleophiles of the reactions of **1**, **2**, **3**, **4**, and **5** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C are summarized in Table 2. The variation trends of DKIEs with X are represented with arrow. The vertical arrows (\uparrow or \downarrow) indicate the direction of the consistent increase of the k_H/k_D values with X. For example, \uparrow indicates that DKIE increases

with a stronger nucleophile. The vertical right-left arrow (\Downarrow) indicates inconsistent variation trends with X.

Solely considering the positive charge of the reaction center P atom (or the inductive effects of the two ligands) in **1-5**, the sequence of the anilinolysis rates should be **1** < **5** < **4** < **2** < **3**. However, the observed sequence is **1** > **2** > **4** > **5** > **3**, giving the rate ratio of 6.0(**1**) : 4.0(**2**) : 2.7(**4**) : 1.3(**5**) : 1(**3**). These results are not consistent with expectations for the positive charge at the reaction center P atom, strongly suggesting that the inductive effects of the two ligands do not play any role to decide the reactivity of anilinolysis of $(R_1O)(R_2O)P(=O)Cl$ -type substrates. The Brønsted coefficients ($\beta_{X(H)}$ and $\beta_{X(D)}$) are in the range of 0.9-1.4. The magnitudes of both $\beta_{X(H)}$ and $\beta_{X(D)}$ values invariably increase as the size of the two ligands becomes greater, however, the $\beta_{X(H)}$ values are somewhat greater than the $\beta_{X(D)}$ values for **1**, **2**, and **3** while the $\beta_{X(D)}$ values are somewhat greater than the $\beta_{X(H)}$ values for **4** and **5**. There are no systematic correlations between (i) $\beta_{X(H \text{ or } D)}$ and k_H/k_D values, (ii) $\beta_{X(H \text{ or } D)}$ values and variation trends of k_H/k_D , and (iii) k_H/k_D values and variation trends of k_H/k_D .

The B3LYP/6-311+G(d,p) geometry, bond angles, and natural bond order (NBO) charges of **3** in the gas phase are shown in Figure 3. The "Degree of distortion" ($\Delta\delta_{GS}$) of the ground state (GS) of substrate with tetracoordinated

Table 2. Summary of Second-Order Rate Constants ($k_H \times 10^3/\text{M}^{-1} \text{ s}^{-1}$)^a with $\text{C}_6\text{H}_5\text{NH}_2$, NBO Charge at the Reaction Center P Atom, Summation of the Taft's Steric Constants of R_1 and R_2 [$\Sigma E_S = E_S(R_1) + E_S(R_2)$],^b Brønsted Coefficients ($\beta_{X(H)}$ and $\beta_{X(D)}$), DKIEs (k_H/k_D), and Variation Trend of DKIEs with Substituent X for the Reactions of **1**, **2**, **3**, **4**, and **5** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in MeCN at 55.0 °C

Substrate	$k_H \times 10^3$	Charge at P	$-\Sigma E_S$	$\beta_{X(H)}/\beta_{X(D)}$	k_H/k_D	Trend	Ref.
1 : (MeO) ₂ P(=O)Cl	4.28	2.226	0.00	0.96/0.91	0.80-0.98	\uparrow	1g
2 : (EtO) ₂ P(=O)Cl	2.82	2.236	0.14	1.06/0.99	0.71-0.92	\uparrow	1g
3 : (<i>i</i> -PrO) ₂ P(=O)Cl	0.710	2.269	0.94	1.10/1.04	0.71-0.95	\Downarrow	this work
4 : (EtO)(PhO)P(=O)Cl	2.00	2.233	2.55	1.13/1.23	1.07-1.28	\downarrow	1f
5 : (PhO) ₂ P(=O)Cl	0.891	2.230	4.96	1.36/1.39	0.61-0.87	\uparrow	1a

^aThe values with unsubstituted aniline. ^bNote that the value of ΣE_S is not $E_S(R_1O) + E_S(R_2O)$ but $E_S(R_1) + E_S(R_2)$ since the data of Taft's steric constants of R_1O are not available.

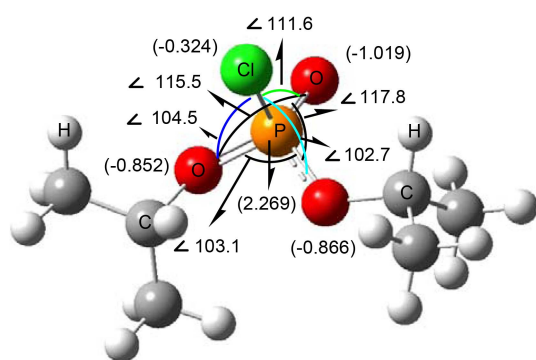


Figure 3. The B3LYP/6-311+G(d,p) geometry of diisopropyl chlorophosphate (**3**) in the gas phase.

phosphorus from the regular tetrahedral structure is defined as eq. (2) by the authors.^{1e,f,4b} The Σ means the sum of all six bond angles, θ_c is the calculated bond angle using the B3LYP/6-311+G(d,p) level, and θ_i is the ideal bond angle (109.5°) of the regular tetrahedral structure.

$$\Delta\delta_{GS} = \Sigma [|\theta_c - \theta_i|/\theta_i] = \Sigma |\theta_c - 109.5|/109.5 \quad (2)$$

The bond angles and degree of distortion ($\Delta\delta_{GS}$) of **1-5** are summarized in Table 3. The MO theoretical structures of the substrates **1-5** show that the three oxygens and chlorine have more or less distorted tetrahedral geometry with the phosphorus atom at the center. The sequence of the degree of distortions is **5** > **4** > **2** \approx **1** > **3**. In the case of **1**, **2**, **4**, and **5**, the degree of distortion is proportional to the size of the two ligands: the greater the size of the two ligands, the greater degree of distortion is observed as expected. In the case of **3**, however, the degree of distortion is exceptionally smallest among five substrates.

The Taft's eq. (3) can be used to rationalize the steric effect on the reaction rate where k is the rate constant, E_S is the Taft's steric constant [$E_S(\text{R}) = 0(\text{Me}); -0.07(\text{Et}); -0.47(i\text{-Pr}); -2.48(\text{Ph})$], ΣE_S is the summation of the steric constant of the ligands, and δ is the sensitivity coefficient.¹¹

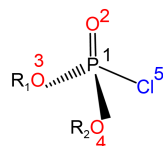
$$\log k = \delta \Sigma E_S + C \quad (3)$$

Buncel reported that the second-order rate constants for the ethanolyse of the three phosphinates, 4-nitrophenyl

dimethyl ($\text{R}_1 = \text{R}_2 = \text{Me}$), methyl phenyl ($\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{Ph}$), and diphenyl ($\text{R}_1 = \text{R}_2 = \text{Ph}$) phosphinates in $\text{R}_1\text{R}_2\text{P}(=\text{O})\text{OC}_6\text{H}_4\text{-4-NO}_2$ -type, gave the relative rates of 235 ($k_{\text{EtO}^-} = 230$): 69 ($k_{\text{EtO}^-} = 67.6$): 1 ($k_{\text{EtO}^-} = 0.980 \text{ M}^{-1} \text{ s}^{-1}$) in anhydrous ethanol at 25.0°C , resulting in $\delta = 0.48$ ($r = 0.953$).¹² Williams reported that the second-order rate constants for the phosphate catalyzed hydrolyses of two phosphinates, 4-nitrophenyl dimethyl and diphenyl phosphinates, gave a relative rate of 52 ($k_{\text{HPO}_4^{2-}} = 1.06 \times 10^{-2}$): 1 ($k_{\text{HPO}_4^{2-}} = 2.05 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$) in 10% dioxane-aqueous 0.1 M NaCl at 25.0°C , resulting in $\delta = 0.35$.¹³ The authors reported that the second-order rate constants for the reactions of the three phosphinic chlorides, dimethyl ($\text{R}_1 = \text{R}_2 = \text{Me}$), methyl phenyl ($\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{Ph}$), and diphenyl ($\text{R}_1 = \text{R}_2 = \text{Ph}$) phosphinic chlorides in $\text{R}_1\text{R}_2\text{P}(=\text{O})\text{Cl}$ -type, with unsubstituted aniline ($\text{C}_6\text{H}_5\text{NH}_2$) in MeCN at 55.0°C gave the relative rate ratio of 4,520 ($k_{\text{H}} = 7,820 \times 10^{-3}$)¹¹: 80 ($k_{\text{H}} = 138 \times 10^{-3}$)¹¹: 1 ($k_{\text{H}} = 1.73 \times 10^{-3}$),¹⁴ resulting in $\delta = 0.74$ ($r = 0.999$). The authors also reported that the second-order rate constants for the anilinolyse of the three phosphinates, 4-nitrophenyl dimethyl ($\text{R}_1 = \text{R}_2 = \text{Me}$), methyl phenyl ($\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{Ph}$), and diphenyl ($\text{R}_1 = \text{R}_2 = \text{Ph}$) phosphinates in $\text{R}_1\text{R}_2\text{P}(=\text{O})\text{OC}_6\text{H}_4\text{-4-NO}_2$ -type, with unsubstituted aniline in DMSO at 60.0°C gave the relative rates of 1.27 ($k_{\text{H}} = 4.06 \times 10^{-4}$): 1.06 ($k_{\text{H}} = 3.37 \times 10^{-4}$): 1 ($k_{\text{H}} = 3.19 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$), resulting in considerably small value of $\delta = 0.02$ ($r = 0.954$).^{1m} These results suggest that the relative reactivities of the phosphinic chlorides and phosphinates are predominantly dependent upon steric effects over the inductive effects of the ligands, and the anilinolysis rates of the phosphinic chloride systems are much more dependent on the steric effects of the ligands compared to anilinolyse and solvolyses of the phosphinate systems.

Figure 4 shows the plot of $\log k_{\text{H}}$ with unsubstituted aniline ($\text{C}_6\text{H}_5\text{NH}_2$) against the summation of the Taft's steric constants of the two ligands of the reactions of five chlorophosphates, **1**, **2**, **3**, **4**, and **5** in MeCN at 55.0°C , according to eq. (3). It should be noted that the value of ΣE_S is not $E_S(\text{R}_1\text{O}) + E_S(\text{R}_2\text{O})$ but $E_S(\text{R}_1) + E_S(\text{R}_2)$ since the data of Taft's steric constants of R_iO are not available. The obtained values of sensitivity coefficients are $\delta = 0.12$ ($r = 0.983$) from **1**, **2**, **4**, and **5**, and $\delta = 0.14$ ($r = 0.999$) from **1**, **4**, and **5**.

Table 3. Bond Angles and Degree of Distortion ($\Delta\delta_{GS}$) of **1-5** in the Gas Phase Calculated at the B3LYP/6-311+G(d,p) Level of Theory^a



Substrate	$\angle 213$	$\angle 214$	$\angle 215$	$\angle 314$	$\angle 315$	$\angle 415$	$\Delta\delta_{GS}$
1: $(\text{MeO})_2\text{P}(=\text{O})\text{Cl}$	118.3	115.5	113.8	102.1	100.3	104.8	0.37
2: $(\text{EtO})_2\text{P}(=\text{O})\text{Cl}$	118.3	115.7	113.6	102.4	102.2	104.5	0.37
3: $(i\text{-PrO})_2\text{P}(=\text{O})\text{Cl}$	115.5	117.8	111.6	103.1	104.5	102.7	0.32
4: $(\text{EtO})(\text{PhO})\text{P}(=\text{O})\text{Cl}$	118.1	116.0	114.1	101.2	100.9	104.3	0.38
5: $(\text{PhO})_2\text{P}(=\text{O})\text{Cl}$	118.5	116.7	113.9	100.7	99.8	104.8	0.40

^aSee ref. 1e for the substrates of **1**, **2**, **4**, and **5**.

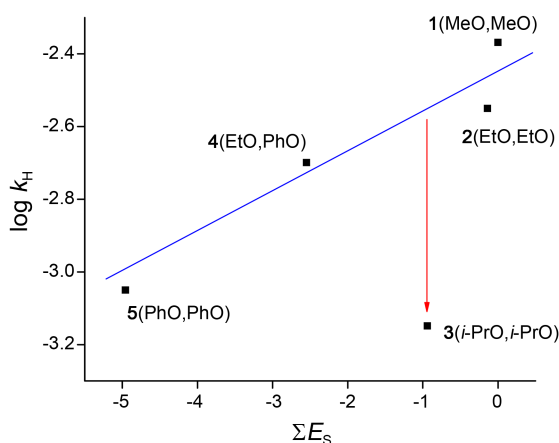
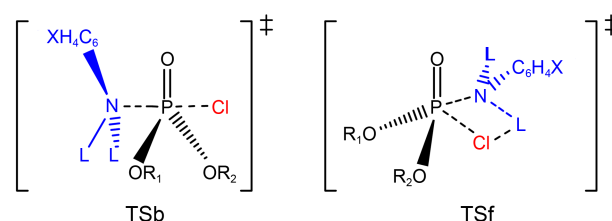


Figure 4. The plot of $\log k_H$ with unsubstituted aniline against ΣE_s of the reactions of **1-5** in MeCN at 55.0 °C. The number of the substrate with the two ligands is displayed next to the corresponding point.

However, the anilinolysis rate of **3** exhibits exceptionally negative deviation from the slope of $\delta = 0.12$ (and 0.14). The substrate **3** has not only the greatest magnitude of the positive charge at the reaction center P atom among five substrates (Table 2) but also smaller size of the two ligands compared to **4** and **5**, and smallest magnitude of the degree of distortion among five substrates (Table 3). This means that the anilinolysis rate of **3** (with two *i*-PrO ligands) is exceptionally slow to be rationalized by the conventional stereoelectronic effects. At this point, the authors tentatively suggest that the exceptionally slow rate of the anilinolysis of **3** is attributed to an unexpected steric hindrance of the two *i*-PrO ligands which cannot be predicted by the Taft's ΣE_s .

Comparing the activation parameters of the reactions of **1-5** with $C_6H_5NH_2$ in MeCN at 55.0 °C in Table 4, the exceptional slow rate of the studied reaction system (**3**) is mainly attributed to the entropy of activation term. There is no correlation between enthalpy of activation (or entropy of activation) and anilinolysis rate.

The DKIEs are one of the strong tools to clarify the reaction mechanism. The DKIEs have provided a useful means to determine the TS structures in the nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures.¹⁸ Incorporation of deuterium in the nucleophile has an advantage in that the α -DKIEs reflect only the degree of bond formation. When partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding, the k_H/k_D



Scheme 2. Backside attack TSb and frontside attack TSf.

values are greater than unity, primary normal ($k_H/k_D > 1.0$).¹⁵ The greater the extent of the hydrogen bond, the value of k_H/k_D becomes greater. In contrast, the DKIEs can only be secondary inverse ($k_H/k_D < 1.0$) in a normal S_N2 reaction, since the N–H(D) vibrational frequencies invariably increase upon going to the TS because of an increase in steric congestion in the bond-making process.¹⁶ The greater the degree of the steric congestion in the TS, the value of k_H/k_D becomes smaller.

The attacking direction of aniline nucleophile can be *semi*-quantitatively divided into three groups on the basis of the magnitudes of the k_H/k_D values: (i) predominant backside attack TSb (Scheme 2) when $k_H/k_D < 1$; (iii) the fraction of the frontside attack TSf (Scheme 2) is greater than that of backside attack TSb when $1.0 < k_H/k_D < 1.1$; (iv) predominant frontside attack TSf when $k_H/k_D > 1.1$.¹⁷

The DKIEs of **1** ($k_H/k_D = 0.80$ - 0.98),^{1g} **2** ($k_H/k_D = 0.71$ - 0.92),^{1g} and **5** ($k_H/k_D = 0.61$ - 0.87)^{1a} are secondary inverse, while those of **4** ($k_H/k_D = 1.0$ - 1.28)^{1f} are primary normal. The authors accordingly proposed that the anilinolyses of **1**, **2**, and **5** proceed through a concerted mechanism involving predominant TSb on the basis of the secondary inverse DKIEs. On the contrary, a concerted mechanism involving predominant hydrogen-bonded four-center-type TSf was proposed for the anilinolysis of **4** on the basis of the large primary normal DKIEs. In the present work, thus, the authors propose a concerted mechanism involving predominant TSb on the basis of the secondary inverse DKIEs.

The variation trends of the DKIEs with X (Table 2) of the anilinolyses of **1**, **2**, and **5** are the same: the weaker the nucleophile, the greater steric hindrance occurs in the TS, the magnitude of the secondary inverse DKIE becomes smaller, and the greater degree of bond formation occurs. In the present work (**3**), however, the magnitudes of the secondary inverse DKIEs invariably increase as X = 4-MeO ($k_H/k_D = 0.877$) < 4-Me ($k_H/k_D = 0.902$) < 3-Me ($k_H/k_D = 0.924$) < H ($k_H/k_D = 0.945$; max) and then invariably de-

Table 4. Activation Parameters of the Reactions of **1-5** with $C_6H_5NH_2$ in MeCN at 55.0 °C^a

Substrate	$\Delta H^\ddagger/\text{kcal mol}^{-1}$	$-\Delta S^\ddagger/\text{cal mol}^{-1}\text{K}^{-1}$	$-T\delta\Delta S^\ddagger/\text{kcal mol}^{-1}$	$\Delta G^\ddagger/\text{kcal mol}^{-1}$
1: (MeO) ₂ P(=O)Cl	6.3	50	16.4	22.7
2: (EtO) ₂ P(=O)Cl	8.6	44	14.4	23.0
3: (<i>i</i> -PrO) ₂ P(=O)Cl ^a	7.2	51	16.7	23.9
4: (EtO)(PhO)P(=O)Cl	6.8	51	16.7	23.3
5: (PhO) ₂ P(=O)Cl	9.7	43	14.1	23.8

^aSee ref. 14.

creases as X = H ($k_{\text{H}}/k_{\text{D}} = 0.945$; max) > 4-F ($k_{\text{H}}/k_{\text{D}} = 0.872$) > 4-Cl ($k_{\text{H}}/k_{\text{D}} = 0.769$) > 3-Cl ($k_{\text{H}}/k_{\text{D}} = 0.709$; min). These results indicate that the degree of bond formation is not systematically changed: (i) in the case of electron-donating substituent X, the stronger the nucleophile, the greater degree of bond formation; (ii) in the case of electron-withdrawing substituent X, the weaker the nucleophile, the greater degree of bond formation. As mentioned earlier, the α -DKIEs reflect only the degree of bond formation in the TS. The authors, thus, postulate that the tightness of the TS is not consistent with the degree of bond formation with X: (i) in the case of electron-donating substituent X, the stronger the nucleophile, the greater the bond formation occurs, and the smaller the degree of bond breaking in the TS as in the anilinolyses of **1**, **2**, and **5**. (ii) in the case of electron-withdrawing substituent X, on the contrary, the weaker the nucleophile, the greater the bond formation occurs, and the smaller the degree of bond breaking in the TS. The primary normal DKIEs of **4** became systematically greater with a weaker nucleophile, denoted as \downarrow , implying that a less basic aniline leads to a greater extent of hydrogen bond formation.

Experimental Section

Materials. Diisopropyl chlorophosphate (97%) and HPLC grade acetonitrile (water content is less than 0.005%) were used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described.¹ Deuterated 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 hours, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ¹H NMR.

Kinetic Procedure. Rates were measured conductometrically at 55.0 °C. The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obsd} were measured by curve fitting analysis in origin program with a large excess of anilines, [Substrate] = 1×10^{-3} M and [X-Aniline] = (0.1-0.5) M. Second-order rate constants, k_2 , were obtained from the slope of a plot of k_{obsd} vs. [X-Aniline] with five concentrations of anilines. The k_{obsd} values were the average of three runs, which were reproducible within $\pm 3\%$.

Product Analysis. Diisopropyl chlorophosphate 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:

(*i*-PrO)₂P(=O)NHC₆H₅. Brown solid; mp (122-123) °C; ¹H NMR (400 MHz, CDCl₃) δ 1.17-1.27 (m, 6H, 2 CH₃, *i*-Pr), 1.33-1.43 (m, 6H, 2 CH₃, *i*-Pr), 4.66-4.70 (m, 2H, 2 CH, *i*-Pr), 5.54, 5.56 (d, $J = 8.8$ Hz, 1H, NH), 6.91-6.97 (m, 3H,

phenyl), 7.21, 7.24 (d, $J = 12.0$ Hz, 2H, phenyl); ¹³C NMR (100 MHz, CDCl₃) δ 23.57, 23.87 (CH₃, *i*-Pr), 71.73 (CH, *i*-Pr), 94.42, 117.33, 121.38, 129.12, 139.91 (C=C, aromatic); ³¹P NMR (162 MHz, CDCl₃) δ 5.07 (s, 1P, P=O); m/z , 257 (M⁺).

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17. This lab has cumulated data of DKIEs for the anilinolyses of various kinds of substrates in MeCN and DMSO.
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