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Kinetics and Mechanism of the Anilinolysis of Dibutyl Chlorothiophosphate in Acetonitrile†

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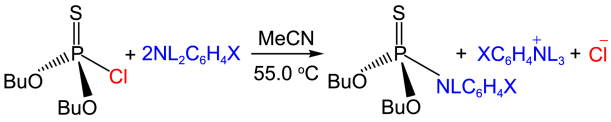
The nucleophilic substitution reactions of dibutyl chlorothiophosphate (**4S**) with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are investigated kinetically in acetonitrile at 55.0 °C. The obtained deuterium kinetic isotope effects (DKIEs; k_H/k_D) are primary normal (k_H/k_D = 1.10-1.35). A concerted mechanism involving predominant frontside nucleophilic attack is proposed on the basis of the primary normal DKIEs and selectivity parameters. Hydrogen bonded, four-center-type transition state is proposed. The steric effects of the two ligands on the anilinolysis rates of the chlorothiophosphates are discussed. The anilinolyses of P=S systems are compared with those of their P=O counterparts on the basis of the reactivities, thio effects, selectivity parameters, and DKIEs.

Key Words : Thiophosphoryl transfer reaction, Anilinolysis, Dibutyl chlorothiophosphate, Deuterium kinetic isotope effect

Introduction

The kinetics and mechanism of the phosphoryl and thiophosphoryl transfer reactions involving tetracoordinated phosphorus atom have been studied extensively by this lab. Continuing the kinetic studies on the thiophosphoryl transfer reactions, the nucleophilic substitution reactions of dibutyl chlorothiophosphate (**4S**) with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are investigated kinetically in acetonitrile (MeCN) at 55.0 ± 0.1 °C (Scheme 1). The aim of this work is to gain further systematic information into the phosphoryl and thiophosphoryl transfer reactions. The kinetic results of the anilinolyses of $(R_1O)(R_2O)P(=S)Cl$-type chlorothiophosphates (dimethyl [**1S**: $(MeO)_2P(=S)Cl$],[1g] diethyl [**2S**: $(EtO)_2P(=S)Cl$],[1g] dipropyl [**3S**: $(PrO)_2P(=S)Cl$],[1x] Y-aryl ethyl [**5S**: $(EtO)(YC_6H_4O)P(=S)Cl$],[1f] and Y-aryl phenyl [**6S**: $(PhO)(YC_6H_4O)P(=S)Cl$][1c] chlorothiophosphates) are compared with those of $(R_1O)(R_2O)P(=O)Cl$-type chlorophosphates (dimethyl [**1O**: $(MeO)_2P(=O)Cl$],[1g] diethyl [**2O**: $(EtO)_2P(=O)Cl$],[1g] dibutyl [**4O**: $(BuO)_2P(=O)Cl$],[1y] Y-aryl ethyl [**5O**: $(EtO)(YC_6H_4O)P(=O)Cl$],[1f] and Y-aryl phenyl [**6O**: $(PhO)(YC_6H_4O)P(=O)Cl$][1a] chlorophosphates). The numbering of the substrates of **1-6** follows the sequence of the summation of the Taft's steric constants[2] (or size) of the two ligands (R_1 and R_2), and **O** and **S** represent the P=O and P=S systems, respectively. Henceforth, for convenience in expressing the substrates, $(R_1O)(R_2O)P(=A)Cl$ is denoted as $A(R_1O,R_2O)$ where R_1 and R_2 are alkyl and/or phenyl (aryl), and A = O or S.

The B3LYP/6-311+G(d,p) geometry, bond angles, and natural bond order (NBO) charges of **4S** in the gas phase[3] are shown in Figure 1. The MO theoretical structure shows that the two oxygens, sulfur, and chlorine have somewhat distorted tetrahedral geometry with the phosphorus atom at the center. The largest and smallest bond angles are 119.0° and 98.6°, respectively, deviation of ca. 10° from the bond angle of 109.5° of the regular tetrahedral structure. The ground state (GS) structure of **4S** in the gas phase does not have plane of symmetry although it has two same ligands of $(BuO)_2$.



Scheme 1. The anilinolysis of dibutyl chlorothiophosphate (**4S**) in MeCN at 55.0 °C.

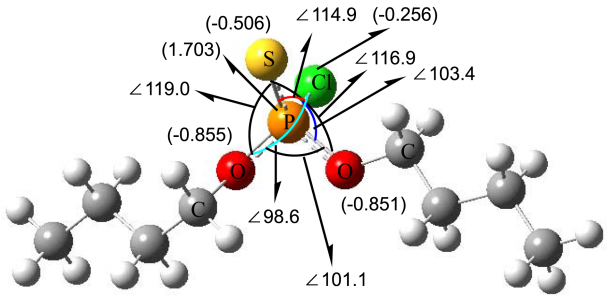


Figure 1. The B3LYP/6-311+G(d,p) geometry of dibutyl chlorothiophosphate (**4S**) in the gas phase.

†This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

Table 1. The Second-Order Rate Constants ($k_{H(D)} \times 10^4$/M^{-1} s^{-1}), Selectivity Parameters (ρ_X and β_X),[a] and DKIEs (k_H/k_D) of the Reactions of Dibutyl Chlorothiophosphate (**4S**) with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C

X	$k_H \times 10^4$	$k_D \times 10^4$	k_H/k_D
4-MeO	27.4 ± 0.1[b]	25.0 ± 0.2	1.10 ± 0.01[g]
4-Me	12.8 ± 0.1	11.1 ± 0.1	1.15 ± 0.01
3-Me	5.59 ± 0.04	4.68 ± 0.02	1.19 ± 0.01
H	3.22 ± 0.01	2.66 ± 0.02	1.21 ± 0.01
3-MeO	1.39 ± 0.01	1.11 ± 0.01	1.25 ± 0.01
4-Cl	0.670 ± 0.003	0.519 ± 0.004	1.29 ± 0.01
3-Cl	0.200 ± 0.001	0.148 ± 0.001	1.35 ± 0.01
$-\rho_{X(H \text{ and } D)}$	3.29 ± 0.03[c]	3.42 ± 0.03[e]	
$\beta_{X(H \text{ and } D)}$	1.17 ± 0.04[d]	1.21 ± 0.04[f]	

[a]The Σ values were taken from ref. 6. The pK_a values of X-anilines in water were taken from ref. 7. [b]Standard deviation. [c]Correlation coefficient, r = 0.999. [d]r = 0.999. [e]r = 0.999. [f]r = 0.999. [g]Standard error {= $1/k_D$ $[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$} from ref. 8.

Results and Discussion

The observed pseudo-first-order rate constants (k_{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 second-order rate constants ($k_{H(D)}$) were determined for 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 1.

$$k_{obsd} = k_0 + k_{H(D)}[XC_6H_4NH_2(D_2)] \quad (1)$$

The k_H and k_D values with X-anilines and deuterated X-anilines, respectively, are summarized in Table 1, together with the DKIEs (k_H/k_D) and Hammett ρ_X and Brönsted β_X selectivity parameters. The pK_a(X) values of the X-anilines in water were used to obtain the Brönsted β_X values in MeCN, and this procedure was justified experimentally and theoretically.[4] The values of pK_a(X) and σ_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 β-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.[5] Thus, the 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 $k_{H(D)}$ *vs* σ_X) and Brönsted [log $k_{H(D)}$ *vs* pK_a(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 primary normal DKIEs ($k_H/k_D > 1$) are observed with all the nucleophiles. The values of DKIEs invariably increase as the nucleophile changes from the strongly to weakly basic anilines; from X = 4-MeO (k_H/k_D = 1.10) to X = 3-Cl (k_H/k_D = 1.35).

The second-order rate constants (k_H) with unsubstituted

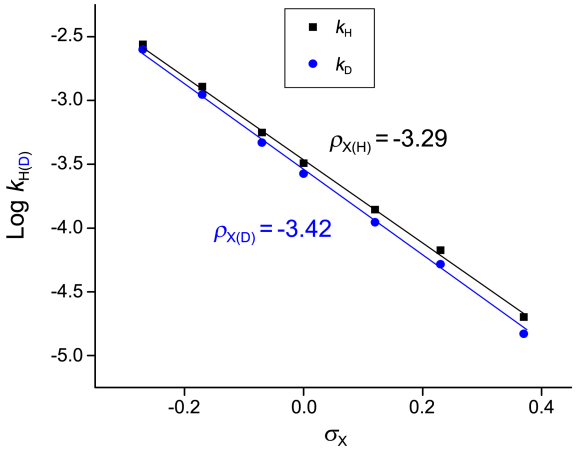


Figure 2. The Hammett plots (log $k_{H(D)}$ *vs* σ_X) of the reactions of dibutyl chlorothiophosphate (**4S**) with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C.

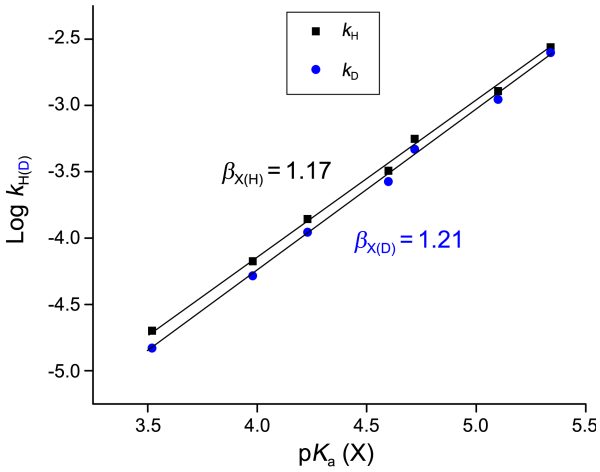


Figure 3. The Brönsted plots [log $k_{H(D)}$ *vs* pK_a(X)] of the reactions of dibutyl chlorothiophosphate (**4S**) with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C.

aniline, NBO charges at the reaction center P atom [B3LYP/6-311+G(d,p) level of theory] in the gas phase,[3] summations of the Taft's steric constants of R_1 and R_2 [$\Sigma E_S = E_S(R_1) + E_S(R_2)$],[2] Brönsted coefficients ($\beta_{X(H)}$), cross-interaction constants (CICs; ρ_{XY}),[9] and DKIEs (k_H/k_D) of the reactions of **1S-6S** with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C are summarized in Table 2. The observed sequence of the anilinolysis rates is **1S** > **2S** > **4S** > **3S** > **5S** > **6S**, giving the relative rates of 9.9(**1S**) : 5.1(**2S**) : 3.2(**4S**) : 3.0(**3S**) : 2.8(**5S**) : 1(**6S**). These results are not consistent with expectations for the positive charge at the reaction center P atom, 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 sequence of the anilinolysis rates of **1S-6S** is almost inversely proportional to the size of the two ligands;[10] the greater the size of the two ligands, the rate becomes slower. These results indicate that the steric effects of the two ligands play an important role to determine the reactivity of the chlorothiophosphate.

The Taft's Eq. (2) can be used to rationalize the steric

Table 2. Summary of the Second-Order Rate Constants ($k_H \times 10^3/M^{-1}\ s^{-1}$) with $C_6H_5NH_2$, NBO Charges at the Reaction Center P Atom, Summations of the Taft's Steric Constants of R_1 and R_2 [$\Sigma E_S = E_S(R_1) + E_S(R_2)$], Brönsted Coefficients ($\beta_{X(H)}$), CICs (ρ_{XY}), and DKIEs (k_H/k_D) for the Reactions of **1S-6S** with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C

substrate	10^3k_H[a]	charge at P	$-\Sigma E_S$[b]	$\beta_{X(H)}$	ρ_{XY}	k_H/k_D	ref.
1S: S(MeO,MeO)	1.09	1.687	0.00	0.993	–	0.945-1.06	1g
2S: S(EtO,EtO)	0.512	1.701	0.14	0.977	–	1.01-1.10	1g
3S: S(PrO,PrO)	0.300	1.702	0.72	1.14	–	1.11-1.35	1x
4S: S(BuO,BuO)	0.322	1.703	0.78	1.17	–	1.10-1.35	this work
5S: S(EtO,YC_6H_4O)	0.280[c]	1.687[c]	2.55[c]	1.10-1.19	-0.28	1.06-1.27	1f
6S: S(PhO,YC_6H_4O)	0.101[c]	1.661[c]	4.96[c]	1.34-1.41	-0.22	1.11-1.33	1c

[a]The values with unsubstituted aniline at 55.0 °C. [b]Note that the value of ΣE_S is not $E_S(R_1O) + E_S(R_2O)$ but $E_S(R_1) + E_S(R_2)$ because of the lack of data of Taft's steric constants of R_iO. [c]The value with Y = H.

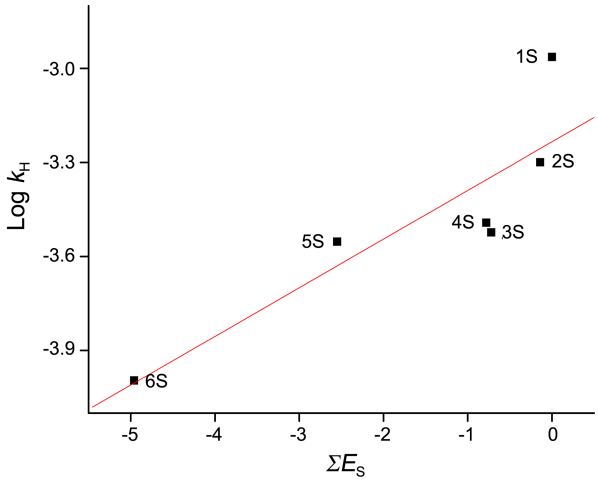


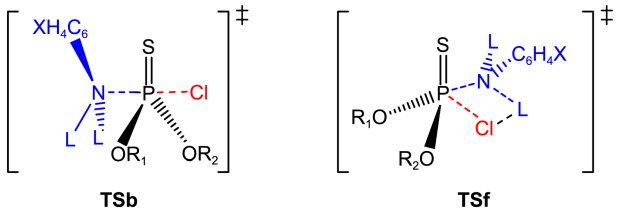
Figure 4. The plot of log k_H *vs* ΣE_S for the reactions of **1S-6S** with $C_6H_5NH_2$ in MeCN at 55.0 °C.

effects of the two ligands on the reaction rate where k_H is the second-order rate constant with unsubstituted aniline in MeCN at 55.0 °C, E_S is the Taft's steric constant [$E_S(R)$ = 0(Me), -0.07(Et), -0.36(Pr), -0.39(Bu), and -2.48(Ph)], ΣE_S is the summation of the steric constants of the two ligands, and δ is the sensitivity coefficient.[2] Herein, it should be noted 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 constant of R_iO is not available. Figure 4 shows the plot of log k_H with unsubstituted aniline ($C_6H_5NH_2$) against the summation of the Taft's steric constants of the two ligands of the reactions of six chlorothiophosphates (**1-6**) in MeCN at 55.0 °C, giving the sensitivity coefficients of: δ = 0.16 (r = 0.878) with six substrates of **1S-6S**; δ = 0.17 (r = 0.915) with five substrates of **1S**, **2S**, **4S**, **5S**, and **6S**; δ = 0.18 (r = 0.959) with four substrates of **1S**, **2S**, **5S**, and **6S**; δ = 0.13 (r = 0.967) with four substrates of **2S**, **4S**, **5S**, and **6S**; and δ = 0.21 (r = 0.998) with three substrates of **1S**, **5S**, and **6S**.

$$\log k_H = \delta\Sigma E_S + C \quad (2)$$

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. 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 values are greater than unity, primary normal ($k_H/k_D > 1.0$).[11] 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.[12] 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 $k_H/k_D < 1$; (ii) the fraction of



Scheme 2. Backside attack TSb and frontside attack TSf (L = H or D).

the frontside attack TSf (Scheme 2) is greater than that of backside attack TSb when $1.0 < k_H/k_D < 1.1$: (iii) predominant frontside attack TSf when $k_H/k_D > 1.1$.

As seen in Table 2, the DKIEs of **1S** (k_H/k_D = 0.95-1.06)[1g] are secondary inverse with the strongly basic anilines and primary normal with the weakly basic anilines, while those of **2S** (k_H/k_D = 1.01-1.10),[1g] **3S** (k_H/k_D = 1.11-1.35), **4S** (k_H/k_D = 1.10-1.35), **5S** (k_H/k_D = 1.06-1.27)[1f] and **6S** (k_H/k_D = 1.11-1.33)[1c] are primary normal. The CICs are also one of the strong tools to clarify the reaction mechanism.[9] The negative values of ρ_{XY} imply that the anilinolyses of **5S** and **6S** proceed through a concerted S_N2 mechanism.[13] The authors accordingly proposed that the anilinolysis of **1S** proceeds through a concerted mechanism and the attacking direction gradually changes from backside to frontside as the aniline changes from the strongly basic to weakly basic. A concerted

Table 3. Comparison of the Anilinolyses of the P=S Systems (**1S**, **2S**, **4S**, **5S**, and **6S**) with those of their P=O Counterparts (**1O**, **2O**, **4O**, **5O**, and **6O**) in MeCN at 55.0 °C

ligands	10^3k_H[a]	charge at P	$\beta_{X(H)}$	ρ_{XY}	k_H/k_D
(MeO,MeO)	1.09/4.28[b]	1.687/2.226[b]	0.99/0.96[b]	–	0.945-1.06/0.80-0.98[b]
(EtO,EtO)	0.512/2.82	1.701/2.236	0.98/1.06	–	1.01-1.10/0.71-0.92
(BuO,BuO)	0.322/2.06	1.703/2.239	1.17/1.11	–	1.10-1.35/0.86-1.10
(EtO,YC_6H_4O)	0.280/2.00	1.687/2.233	1.10-1.19/1.09-1.20	-0.28/-0.60[b]	1.06-1.27/1.07-1.28
(PhO,YC_6H_4O)	0.101/0.891	1.661/2.230	1.34-1.41/1.24-1.68	-0.22/-1.31	1.11-1.33/0.61-0.87

[a]The value with unsubstituted aniline ($k_H \times 10^3/M^{-1}\ s^{-1}$). [b]The value of P=S/its counterpart P=O system.

mechanism was proposed for the anilinolysis of **2S** in which the fraction of the frontside attack TSf is greater than that of backside attack TSb on the basis of $1.01 < k_H/k_D < 1.10$. A concerted mechanism involving predominant hydrogen-bonded, four-center-type TSf was proposed for the anilinolyses of **3S**, **5S**, and **6S** on the basis of the large primary normal DKIEs. In the present work of **4S**, thus, the authors propose a concerted mechanism involving predominant hydrogen-bonded, four-center-type TSf on the basis of the primary normal DKIEs.

The second-order rate constants, NBO charges at the reaction center P atom, Brönsted coefficients ($\beta_{X(H)}$), CICs (ρ_{XY}), and DKIEs (k_H/k_D) for the reactions of P=S systems and their P=O counterparts with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C are summarized in Table 3 to compare both systems. The sequence of the anilinolysis rates of the P=O systems are inversely proportional to the size of the two ligands, indicating that the steric effects are the dominant factor over the inductive effects of the two ligands. The anilinolysis rates of the P=O systems are 4-9 times faster than their P=S counterparts: k_H(**1O**)/k_H(**1S**) = 3.9; k_H(**2O**)/k_H(**2S**) = 5.5; k_H(**4O**)/k_H(**4S**) = 6.4; k_H(**5O**)/k_H(**5S**) = 7.1; k_H(**6O**)/k_H(**6S**) = 8.8. The ratio of k_H(**O**)/k_H(**S**) increases as the size of the ligands becomes larger, indicating that the P=S systems are more sensitive to the steric effects of the two ligands compared to the P=O systems, i.e., k_H(**1O**)/k_H(**6O**) = 4.8 and k_H(**1S**)/k_H(**6S**) = 10.8. It is well known that the P=O systems are generally 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 and favors P=O over P=S.[14] The magnitude of the positive charge of the reaction center P atom for the P=O system are greater (0.54-0.57; see third column in Table 3) than that for its P=S counterpart system which may represent the electronegativity difference between O and S, although the calculated NBO charges are not in MeCN but in the gas phase. There is no consistency for both systems between: (i) $\beta_{X(H)}$ and ρ_{XY}; (ii) $\beta_{X(H)}$ and k_H/k_D; $\beta_{X(H)}$ and the attacking direction of nucleophile. The sign of ρ_{XY} of **5O** and **6O** is negative, the same as in **5S** and **6S**, which indicates the S_N2 mechanism. However the magnitudes of ρ_{XY} of **5O** and **6O** are greater than those of **5S** and **6S**, suggesting that the degree of bond formation of P=O system is greater than that of P=S system.[13] The DKIEs of the P=S systems are primary normal except **1S** with the weakly basic anilines while those of the P=O systems are secondary inverse except **4O** with the weakly basic anilines and **5O**. The fraction of the frontside nucleophilic attack of the P=S system is greater than that of the P=O system because of the greater electrophilicity of reaction center P in P=O compared to P=S. In other words, when the degree of steric hindrance is more or less significant, the lesser electrophilicity of P in P=S leads to a frontside attack with a hydrogen bonded four-center-type TSf rather than a backside attack. Meanwhile, the greater electrophilicity of P in P=O overcomes the steric hindrance and enables a backside attack until the severe steric hindrance prohibits backside attack and consequently frontside attack becomes predominant.[15]

Experimental Section

Materials. Dibutyl chlorothiophosphate (commercially available) 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.[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 hr, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ^{1}H 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 pseudo-first-order rate constant values (k_{obsd}) were the average of at least three runs that were reproducible within ± 3%.

Product Analysis. Dibutyl chlorothiophosphate 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 $MgSO_4$. 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 'Supplementary Materials'):

$(BuO)_2P(=S)NHC_6H_5$. Brown liquid; ^{1}H-NMR (400

MHz, $CDCl_3$) δ 0.80-0.92 (m, 6H, 2 CH_3, Bu), 1.30-1.40 (m, 4H, 2 CH_2, Bu), 1.59-1.66 (m, 4H, 2 CH_2, Bu), 3.93-4.02 (m, 2H, OCH_2, BuO), 4.08-4.16 (m, 2H, OCH_2, BuO), 5.04 (s, 1H, NH), 6.94-6.98 (t, J = 7.6 Hz, 3H, phenyl), 7.20-7.26 (d, J = 7.2 Hz, 2H, phenyl); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.47 (CH_3, Bu), 18.70 (CH_2, Bu), 31.83, 31.91 (CH_2, Bu), 66.62, 66.90 (OCH_2, BuO), 117.33, 117.59, 121.97, 129.19, 139.39 (C=C, aromatic); ^{31}P-NMR (162 MHz, $CDCl_3$) δ 70.77 (s, 1P, P=S); MS (EI) *m*/*z* 301 (M^+).

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