Kinetics and Mechanism of Anilinolyses of Aryl Methyl and Aryl Propyl Chlorothiophosphates in Acetonitrile[†]

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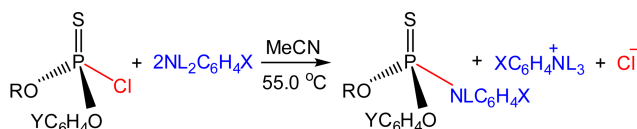
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Nucleophilic substitution reactions of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates with substituted anilines and deuterated anilines are investigated kinetically in acetonitrile at 55.0 $^\circ$C. A concerted mechanism is proposed for **8** based on the negative ρ_{XY} (= –0.23) value, while a stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed for **10** based on the positive ρ_{XY} (= +0.68) value. The deuterium kinetic isotope effects (DKIEs; k_H/k_D) are 0.89-1.28 and 0.62-1.20 with **8** and **10**, respectively. Primary normal and secondary inverse DKIEs are rationalized by a frontside attack involving hydrogen bonded, four-center-type transition state and backside attack involving in-line-type transition state, respectively.

Key Words : Thiophosphoryl transfer reaction, Anilinolysis, Y-Aryl methyl and Y-aryl propyl chlorothiophosphates, Deuterium kinetic isotope effect, Cross-interaction constant

Introduction

As final part on going kinetic studies on the anilinolyses of the chlorothiophophates [$(R_1O)(R_2O)P(=S)Cl$-type where R_1 = R_2 = alkyl and/or aryl], the reactions of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) have been kinetically investigated in acetonitrile (MeCN) at 55.0 ± 0.1 $^\circ$C (Scheme 1). The aim of this work is to obtain further information on the thiophosphoryl transfer reactions by comparing the anilinolyses of the following chlorothiophosphates in terms of the selectivity parameters, steric effects of the two ligands on the rate, reaction mechanism, deuterium kinetic isotope effects (DKIEs) and activation parameters: dimethyl [**1**: $(MeO)_2P(=S)Cl$],[1a] ethyl methyl [**2**: $(MeO)(EtO)P(=S)Cl$],[1b] diethyl [**3**: $(EtO)_2$-$P(=S)Cl$],[1a] ethyl propyl [**4**: $(EtO)(PrO)P(=S)Cl$],[1b] dipropyl [**5**: $(PrO)_2P(=S)Cl$],[1c] dibutyl [**6**: $(BuO)_2P(=S)Cl$],[1d] diisopropyl (**7**: $(i$-$PrO)_2P(=S)Cl$],[1b] Y-aryl ethyl [**9**: $(EtO)(YC_6H_4O)$-$P(=S)Cl$],[1e] Y-aryl phenyl [**11**: $(PhO)(YC_6H_4O)P(=S)Cl$][1f] and Y-aryl 4-chlorophenyl [**12**: $(4$-Cl-$C_6H_4O)(YC_6H_4O)$-$P(=S)Cl$][1f] chlorothiophosphates. **1-12** are numbered according to the sequence of the summation of the Taft steric constants of the two ligands (R_1 and R_2).[2,3]

Results and Discussion

Tables 1-3 list the second-order rate constants ($k_H/M^{-1}\ s^{-1}$), $\rho_{X(H)}$ and $\beta_{X(H)}$ with X, and $\rho_{Y(H)}$ with Y, respectively, of the reactions of **8** and **10** with X-anilines. The substituent effects of X and Y on the reaction rates are compatible with a typical nucleophilic substitution reaction and the rate increases with more basic aniline and with more electron-withdrawing substituent Y. The rates of **8** are 2-7 times faster than those of **10** depending on X and/or Y. The free energy relationships with X and Y are all linear. The Hammett (Figs. S1 and S2 with **8** and **10**, respectively) and Brönsted (Figs. S3 and S4 with **8** and **10**, respectively) plots for substituent X variations in the nucleophiles, and Hammett plots (Figs. S5 and S6 with **8** and **10**, respectively) for substituent Y variations in the substrates are shown in the supporting information. The magnitudes of the $\rho_{X(H)}$ (= –2.60 to –2.51) and $\beta_{X(H)}$ (= 0.89-0.93) values with **8** are somewhat smaller than those ($\rho_{X(H)}$ = –3.30 to –2.97 and $\beta_{X(H)}$ = 1.05-1.17) with **10**. The $\rho_{Y(H)}$ (= 0.60-0.78) values with **8** are more or less smaller than those ($\rho_{Y(H)}$ = 0.62-1.04) with **10**. This may suggest that the degrees of both bond formation and cleavage with **10** are greater than those with **8** in the transition state (TS). The $\rho_{X(H)}$ values invariably decrease (*i.e.*, more negative value; $\partial\rho_{X(H)} < 0$) with **8**, whereas those invariably increase (*i.e.*, less negative value; $\partial\rho_{X(H)} > 0$) with **10** as substituent Y becomes more electron-withdrawing ($\partial\sigma_Y > 0$). Meanwhile, the $\rho_{Y(H)}$ values consistently decrease (*i.e.*, less positive value; $\partial\rho_{Y(H)} < 0$) with **8**, whereas those consistently increase with **10** (*i.e.*, more positive value;

R = Me (**8**), Pr (**10**) ; L = H, D
X = 4-MeO, 4-Me, 3-Me, H, 4-Cl, 3-Cl; Y = 4-MeO, 4-Me, H, 3-MeO, 4-Cl

Scheme 1. Reactions of Y-aryl methyl (**8**) and Y-aryl propyl (**10**) chlorothiophosphates with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 $^\circ$C.

$\partial\rho_{Y(H)} > 0$) as the pyridine becomes less basic ($\partial\sigma_X > 0$). Note that the variation trends of the $\rho_{X(H)}$ values for substituent X variations in the nucleophiles and $\rho_{Y(H)}$ values for substituent Y variations in the substrates with **8** is opposite to those with **10**, resulting in $\partial\rho_{X(H)}/\partial\sigma_Y = (-)/(+) < 0$ and $\partial\rho_{Y(H)}/\partial\sigma_X = (-)/(+) < 0$ with **8**, while $\partial\rho_{X(H)}/\partial\sigma_Y = (+)/(+) > 0$ and $\partial\rho_{Y(H)}/\partial\sigma_X$

$= (+)/(+) > 0$ with **10** (*vide infra*).

Table 4 summarizes the second-order rate constants (k_H) with unsubstituted aniline, natural bond order (NBO) charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory], summations of the Taft steric constants of R_1 and R_2 [$\Sigma E_S = E_S(R_1) + E_S(R_2)$],[2,3] Brönsted

Table 1. Second-Order Rate Constants ($k_H \times 10^4/M^{-1}$ s^{-1}) of the Reactions of **8** and **10** with $XC_6H_4NH_2$ in MeCN at 55.0 ^{o}C

substrate	X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
8	4-MeO	42.5 ± 0.2	49.0 ± 0.1	60.7 ± 0.3	80.8 ± 0.3	105 ± 1
	4-Me	17.1 ± 0.1	19.0 ± 0.1	25.8 ± 0.2	30.9 ± 0.3	39.3 ± 0.2
	3-Me	7.83 ± 0.03	8.64 ± 0.1	10.2 ± 0.1	13.2 ± 0.1	16.5 ± 0.2
	H	5.32 ± 0.03	6.45 ± 0.04	7.85 ± 0.01	8.49 ± 0.01	12.1 ± 0.1
	4-Cl	1.74 ± 0.02	1.97 ± 0.01	2.37 ± 0.02	2.89 ± 0.01	3.79 ± 0.01
	3-Cl	0.914 ± 0.001	1.04 ± 0.01	1.23 ± 0.01	1.45 ± 0.01	1.90 ± 0.03
10	4-MeO	19.2 ± 0.1	22.3 ± 0.2	25.4 ± 0.2	30.2 ± 0.1	41.7 ± 0.1
	4-Me	6.44 ± 0.02	7.40 ± 0.2	7.97 ± 0.01	9.75 ± 0.01	15.4 ± 0.2
	3-Me	2.15 ± 0.01	2.59 ± 0.02	3.05 ± 0.02	3.77 ± 0.01	5.69 ± 0.01
	H	1.55 ± 0.01	1.81 ± 0.01	2.04 ± 0.01	2.63 ± 0.01	4.09 ± 0.01
	4-Cl	0.320 ± 0.003	0.402 ± 0.001	0.495 ± 0.001	0.717 ± 0.001	1.02 ± 0.01
	3-Cl	0.126 ± 0.001	0.163 ± 0.001	0.205 ± 0.001	0.284 ± 0.001	0.454 ± 0.001

Table 2. Hammett ($\rho_{X(H)}$) and Brönsted ($\beta_{X(H)}$) Coefficients[a] with X of the Reactions of **8** and **10** with $XC_6H_4NH_2$ in MeCN at 55.0 ^{o}C

substrate	Y	4-MeO	4-Me	H	3-MeO	4-Cl
8	$-\rho_{X(H)}$	2.51 ± 0.10	2.51 ± 0.10	2.56 ± 0.11	2.62 ± 0.12	2.60 ± 0.12
	$\beta_{X(H)}$	0.89 ± 0.11	0.89 ± 0.10	0.91 ± 0.10	0.93 ± 0.12	0.93 ± 0.12
10	$-\rho_{X(H)}$	3.30 ± 0.11	3.22 ± 0.12	3.13 ± 0.12	3.00 ± 0.12	2.97 ± 0.11
	$\beta_{X(H)}$	1.17 ± 0.11	1.14 ± 0.11	1.11 ± 0.12	1.07 ± 0.12	1.05 ± 0.11

[a]Correlation coefficients (r) of the $\rho_{X(H)}$ and $\beta_{X(H)}$ values are better than 0.986.

Table 3. Hammett Coefficients ($\rho_{Y(H)}$)[a] with Y of the Reactions of **8** and **10** with $XC_6H_4NH_2$ in MeCN at 55.0 ^{o}C

substrate\X	4-MeO	4-Me	3-Me	H	4-Cl	3-Cl
8	0.78 ± 0.03	0.74 ± 0.01	0.64 ± 0.03	0.64 ± 0.04	0.64 ± 0.03	0.60 ± 0.03
10	0.62 ± 0.04	0.66 ± 0.07	0.77 ± 0.05	0.77 ± 0.06	0.96 ± 0.04	1.04 ± 0.05

[a]Correlation coefficients (r) of $\rho_{Y(H)}$ values are better than 0.983.

Table 4. Summary of the Second-Order Rate Constants ($k_H \times 10^4/M^{-1}$ s^{-1}) with $C_6H_5NH_2$, NBO Charges at the Reaction Center P Atom, $\Sigma E_S = E_S(R_1) + E_S(R_2)$, $\beta_{X(H)}$, $\rho_{XY(H)}$, k_H/k_D and Variation Trends of k_H/k_D with X and Y for the Reactions of **1-12** with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 ^{o}C

| substrate	$10^4 k_H$	charge at P	$-\Sigma E_S$	$\beta_{X(H)}$	$\rho_{XY(H)}$	k_H/k_D	trend
1: $(MeO)_2P(=S)Cl$	10.9	1.687	0.00	0.99	–	0.95-1.06	↑
2: $(MeO)(EtO)P(=S)Cl$	8.44	1.693	0.07	0.79	–	0.66-0.99	↑
3: $(EtO)_2P(=S)Cl$	5.12	1.701	0.14	0.98	–	1.01-1.10	↑
4: $(EtO)(PrO)P(=S)Cl$	3.89	1.700	0.43	0.93	–	0.78-1.19	↓
5: $(PrO)_2P(=S)Cl$	3.00	1.702	0.72	1.14	–	1.11-1.35	↓
6: $(BuO)_2P(=S)Cl$	3.22	1.703	0.78	1.17	–	1.10-1.35	↓
7: $(i\text{-}PrO)_2P(=S)Cl$	2.02	1.723	0.94	0.87	–	1.06-1.21	↓
8: $(MeO)(YC_6H_4O)P(=S)Cl$	7.85^a	1.686^a	2.48^a	0.89-0.93	−0.23	0.89-1.28	↓→
9: $(EtO)(YC_6H_4O)P(=S)Cl$	2.80^a	1.687^a	2.55^a	1.10-1.19	−0.28	1.06-1.27	↓→
10: $(PrO)(YC_6H_4O)P(=S)Cl$	2.04^a	1.687^a	2.84^a	1.05-1.17	+0.68	0.62-1.20	↑→
11: $(PhO)(YC_6H_4O)P(=S)Cl$	1.01^a	1.661^a	4.96^a	1.34-1.41	−0.22	1.11-1.33	↓→
12: $(4\text{-}Cl\text{-}C_6H_4O)(YC_6H_4O)P(=S)Cl$	1.48^a	1.667^a	$> 4.96^a$	1.23-1.48	−0.50	1.10-1.46	↓→

[a]Y = H.
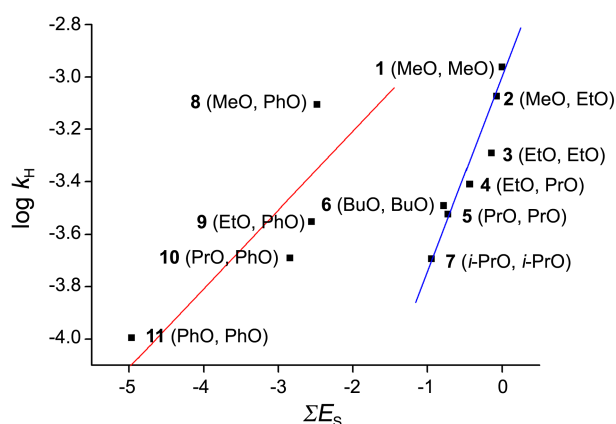
Figure 1. Taft plot of log k_H *vs* ΣE_S for the reactions of **1-11** with $C_6H_5NH_2$ in MeCN at 55.0 °C. The number of the substrate and two ligands of R_1O and R_2O are displayed next to the corresponding point.

coefficients ($\beta_{X(H)}$), cross-interaction constants (CICs; $\rho_{XY(H)}$),[4] DKIEs (k_H/k_D) and variation trends of the k_H/k_D values with X in the nucleophiles and with Y in the substrates for the reactions of **1-12** with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C. The variation trends of the k_H/k_D values with X and Y are represented by an vertical and horizontal arrows, respectively. The vertical ($\uparrow$ or $\downarrow$) and horizontal arrows ($\rightarrow$ or $\leftarrow$) indicate the direction of the consistent increase in the k_H/k_D value with X and Y, respectively. For example, $\uparrow$ indicates an increase of the k_H/k_D value with a more electron-donating X, and $\rightarrow$ indicates an increase of the k_H/k_D value with a more electron-withdrawing Y.

The sequence of the anilinolysis rates of **1-11** is not consistent with expectations for the positive NBO charge at the reaction center P atom, indicating that the inductive effects of the two ligands are not major factor to decide the anilinolysis rates of the chlorothiophosphates. According to Taft Eq. of 'log $k_H = \delta\Sigma E_S + C$', Figure 1 shows the Taft plot of log k_H (with $C_6H_5NH_2$) against the summation of the Taft steric constants of the two ligands for the anilinolyses of **1-11** in MeCN at 55.0 °C, giving the sensitivity coefficients of $\delta = 0.65 \pm 0.09$ (r = 0.948) and $\delta = 0.25 \pm 0.27$ (r = 0.803) with seven substrates of **1-7** (*a* group containing two alkoxy ligands) and four substrates of **8-11** [*b* group containing phenoxy ligand(s)], respectively.[5] It is worthy of note that: (i) the sequence of the anilinolysis rates is inversely proportional (roughly) to the size of the two ligands; (ii) but divided into two groups; *a* group of **1-7** and *b* group of **8-11**; and (iii) the correlation coefficient with *b* group is not good. The steric effects of the two ligands on the anilinolysis rates of the P=O counterparts, chlorophosphates [$(R_1O)(R_2O)$-$P(=O)Cl$-type], show the same trends as those of the chlorothiophosphates.[1a,e,6] These indicate that the steric effects of the two ligands on the anilinolysis rates of chloro(thio)phosphates play an important role and that *a* group is 'very different' from *b* group regarding the steric effects of the two ligands on the rate.[7]

Figure 2 shows the $\rho_{XY(H)}$ values for the reactions of **8** and **10** with X-anilines in MeCN at 55.0 °C, based on the defini-
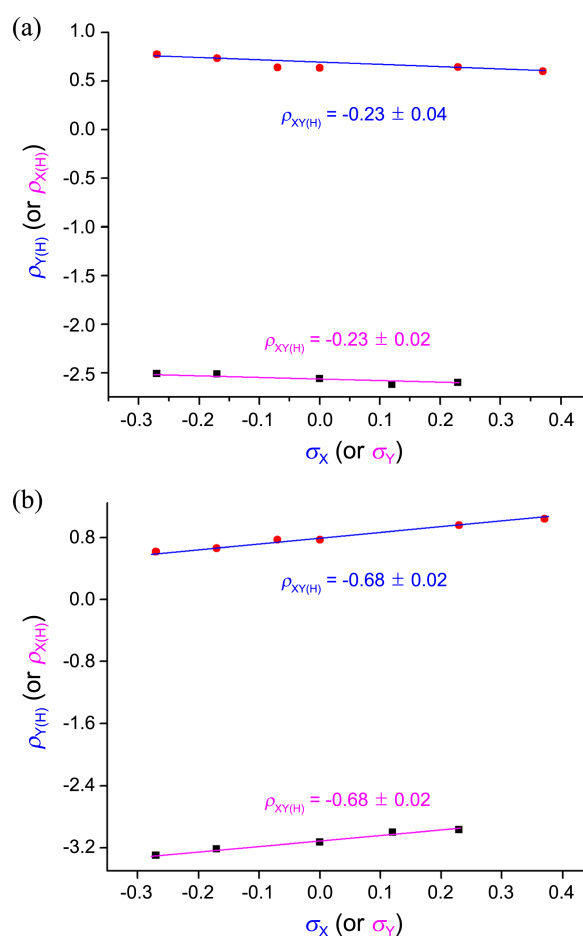

Figure 2. Plots of $\rho_{X(H)}$ *vs* σ_Y and $\rho_{Y(H)}$ *vs* σ_X of the reactions of **8** and **10** with $XC_6H_4NH_2$ in MeCN at 55.0 °C. The obtained $\rho_{XY(H)}$ values by multiple regression are: (a) $\rho_{XY(H)} = -0.23 \pm 0.10$ (r = 0.976) with **8**; (b) $\rho_{XY(H)} = +0.68 \pm 0.11$ (r = 0.980) with **10**.

tion of the CIC: log $(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y$, hence, $\rho_{XY} = \partial^2\log(k_{XY}/k_{HH})/(\partial\sigma_X\partial\sigma_Y) = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$.[4] The signs of the $\rho_{XY(H)}$ are negative ($\rho_{XY(H)} = -0.23$) and positive ($\rho_{XY(H)} = +0.68$) for **8** and **10**, respectively (*vide supra*). Thus, a concerted mechanism is proposed for **8** while a stepwise mechanism with a rate-limiting leaving group departure from the intermediate for **10**, because the ρ_{XY} has a negative value in a concerted S_N2 (or a stepwise mechanism with a rate-limiting bond formation) and a positive value for a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate.[4] The degree of tightness of the TS structure with **10** is greater than that with **8** because the magnitude of ρ_{XY} is inversely proportional to the distance between X and Y through the reaction center.[4,8]

Tables 5 and 6 list the second-order rate constants (k_D/M^{-1} s^{-1}) with the deuterated anilines ($XC_6H_4ND_2$) and DKIEs (k_H/k_D) with **8** and **10** in MeCN at 55.0 °C, respectively. The DKIEs show primary normal ($k_H/k_D > 1$) and secondary inverse ($k_H/k_D < 1$) depending on the substituents X and/or Y for both **8** ($k_H/k_D = 0.89$-1.28) and **10** ($k_H/k_D = 0.62$-1.20). The variation trends of the k_H/k_D values with Y are the same for both **8** and **10**, and the k_H/k_D values become larger with a

Table 5. Second-Order Rate Constants ($k_D \times 10^4/M^{-1}\,s^{-1}$) of the Reactions of **8** and **10** with $XC_6H_4ND_2$ in MeCN at 55.0 °C

substrate	X\Y	4-MeO	4-Me	H	3-MeO	4-Cl
8	4-Me	19.3 ± 0.1	20.5 ± 0.1	27.4 ± 0.1	32.8 ± 0.2	39.4 ± 0.1
	H	4.90 ± 0.01	5.75 ± 0.01	7.01 ± 0.01	7.14 ± 0.01	9.88 ± 0.01
	4-Cl	1.48 ± 0.01	1.63 ± 0.01	1.93 ± 0.01	2.34 ± 0.01	2.96 ± 0.01
10	4-MeO	21.6 ± 0.1	23.1 ± 0.3	25.3 ± 0.1	26.9 ± 0.1	34.8 ± 0.1
	4-Me	7.34 ± 0.01	7.93 ± 0.01	8.03 ± 0.01	8.95 ± 0.01	13.5 ± 0.2
	3-Me	2.55 ± 0.02	2.79 ± 0.01	3.08 ± 0.01	3.57 ± 0.01	5.18 ± 0.01
	H	1.86 ± 0.01	2.03 ± 0.01	2.06 ± 0.01	2.51 ± 0.01	3.04 ± 0.01
	4-Cl	0.422 ± 0.001	0.459 ± 0.001	0.504 ± 0.001	0.703 ± 0.001	0.971 ± 0.001
	3-Cl	0.203 ± 0.001	0.221 ± 0.001	0.250 ± 0.001	0.285 ± 0.001	0.440 ± 0.001

Table 6. DKIEs (k_H/k_D) of the Reactions of **8** and **10** with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 °C

substrate	X\Y	4-MeO	4-Me	H	3-MeO	4-Cl
8	4-Me	0.886 ± 0.007	0.927 ± 0.007	0.942 ± 0.008	0.973 ± 0.011	0.997 ± 0.006
	H	1.09 ± 0.01	1.12 ± 0.01	1.12 ± 0.01	1.19 ± 0.01	1.22 ± 0.01
	4-Cl	1.18 ± 0.02	1.21 ± 0.01	1.22 ± 0.01	1.24 ± 0.01	1.28 ± 0.01
10	4-MeO	0.889 ± 0.006	0.965 ± 0.015	1.00 ± 0.01	1.12 ± 0.01	1.20 ± 0.01
	4-Me	0.877 ± 0.003	0.933 ± 0.003	0.993 ± 0.002	1.09 ± 0.01	1.14 ± 0.02
	3-Me	0.843 ± 0.008	0.928 ± 0.008	0.990 ± 0.007	1.06 ± 0.01	1.10 ± 0.01
	H	0.833 ± 0.007	0.892 ± 0.007	0.990 ± 0.007	1.05 ± 0.01	1.07 ± 0.01
	4-Cl	0.758 ± 0.007	0.876 ± 0.003	0.982 ± 0.003	1.02 ± 0.01	1.05 ± 0.01
	3-Cl	0.621 ± 0.006	0.738 ± 0.006	0.820 ± 0.005	0.997 ± 0.005	1.03 ± 0.01

[a]Standard error {= $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$}.

more electron-withdrawing Y, noted as horizontal arrow of → in Table 4. In contrast, the variation trends of the k_H/k_D values with X for **8** are opposite to those for **10**: the k_H/k_D values become larger with a more electron-withdrawing X for **8** (↓), whereas those become larger with a more electron-donating X for **10** (↑), noted as vertical arrows in Table 4. At a glance, the variation trends of the k_H/k_D values with X and/or Y could be one of the strong tools to clarify the reaction mechanism: (i) **8**, **9**, **11** and **12**, *via* a S_N2 mechanism, show the variation trends of ↓→; (ii) while **10**, *via* a stepwise mechanism with a rate-limiting bond cleavage, shows ↑←. However, the variation trends of the k_H/k_D values with X and/or Y cannot be the supporting evidence to substantiate the mechanism based on: (i) the anilinolysis of Y-aryl phenyl chlorophosphates, *via* a S_N2 mechanism ($\rho_{XY(H)} = -1.31$), showing ↑←;[6a] (ii) Y-aryl ethyl chlorophosphates, *via* a S_N2 mechanism ($\rho_{XY(H)} = -0.60$), showing ↓→;[1e] (iii) Y-aryl 4-chlorophenyl chlorophosphates, *via* a S_N2 mechanism ($\rho_{XY(H)} = -0.31$), showing ↑←;[6b] (iv) *O*-aryl methyl phosphono-chloridothioates, *via* a S_N2 and stepwise mechanism with a rate-limiting bond cleavage ($\rho_{XY(H)} = -0.95$ and 0.77 with strongly and weakly basic anilines, respectively), showing ↑→;[9a] (v) Y-aryl phenyl isothiocyanophsphates, *via* a stepwise mechanism with a rate-limiting bond cleavage and S_N2 ($\rho_{XY(H)} = 1.41$ and -0.18 with the strongly and weakly basic anilines, respectively), showing ↑→;[9b] (vi) Y-aryl ethyl isothiocyanophsphates, *via* a S_N2 and stepwise mechanism with a rate-limiting bond cleavage ($\rho_{XY(H)} = -0.14$ and 3.89 with the strongly and weakly basic anilines, respectively), show-

ing ↑→.[9c] The $\beta_{X(H)}$ values of **1-12** are relatively large in the range of 0.8-1.5, and this indicates that it could be sometimes dangerous to suggest the reaction mechanism based on the $\beta_{X(H)}$ values.

When partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding (*e.g.* TSf in Scheme 2), the k_H/k_D values are greater than unity, primary normal ($k_H/k_D > 1.0$).[10] In contrast, the DKIEs can only be secondary inverse ($k_H/k_D < 1.0$) when an increase in the steric congestion occurs in the bond-making process (*e.g.* TSb in Scheme 2), because the N–H(D) vibrational frequencies invariably increase upon going to the TS.[11] In this respect, primary normal and secondary inverse DKIEs are rationalized by a frontside equatorial attack involving hydrogen bonded four-center-type TSf and backside apical attack involving in-line-type TSb, respectively. In the case of **10**, the min value of $k_H/k_D = 0.62$ with X = 3-Cl and Y = 4-MeO indicates severe steric congestion in the TS. Table R1 lists six substrates, showing $(k_H/k_D)_{min} < 0.62$, studied in this lab.[12] As seen in Table R1, there are no consistent relationships
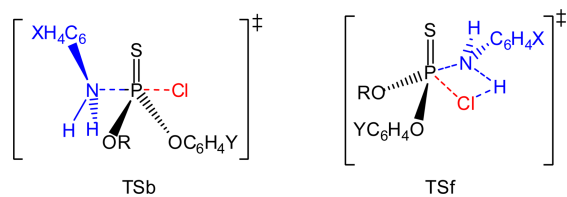

Scheme 2. Backside attack involving in-line-type TSb and frontside attack involving a hydrogen bonded, four-center-type TSf.

Table 7. Second-Order Rate Constants ($k_H/M^{-1} s^{-1}$) and Activation Parameters[a] for the Reactions of **8** with $XC_6H_4NH_2$ (X = 4-MeO, H, 4-Cl) in MeCN

Y	X	$k_H \times 10^4/M^{-1} s^{-1}$			$\Delta H^{\neq}/$ kcal mol^{-1}	$-\Delta S^{\neq}/$ cal mol^{-1} K^{-1}
		45.0 °C	55.0 °C	65.0 °C		
4-MeO	4-MeO	29.1 ± 0.4	42.5 ± 0.2	60.8 ± 0.1	7.2 ± 0.1	48 ± 1
	H	3.52 ± 0.01	5.32 ± 0.03	8.20 ± 0.01	8.4 ± 0.3	48 ± 1
	4-Cl	1.07 ± 0.01	1.74 ± 0.02	2.70 ± 0.01	9.3 ± 0.2	48 ± 1
4-Me	4-MeO	31.4 ± 0.1	49.0 ± 0.1	72.5 ± 0.8	8.3 ± 0.1	44 ± 1
	H	4.00 ± 0.02	6.45 ± 0.04	10.7 ± 0.1	9.8 ± 0.4	43 ± 1
	4-Cl	1.15 ± 0.02	1.97 ± 0.01	3.24 ± 0.01	10.4 ± 0.1	44 ± 1
H	4-MeO	39.0 ± 0.1	60.7 ± 0.3	94.4 ± 0.2	8.8 ± 0.2	42 ± 1
	H	4.92 ± 0.01	7.85 ± 0.01	13.1 ± 0.1	9.8 ± 0.5	43 ± 1
	4-Cl	1.43 ± 0.01	2.37 ± 0.02	3.88 ± 0.01	10.0 ± 0.1	45 ± 1
3-MeO	4-MeO	52.5 ± 0.4	80.8 ± 0.3	123 ± 1	8.5 ± 0.1	43 ± 1
	H	5.41 ± 0.01	8.49 ± 0.01	12.9 ± 0.1	8.6 ± 0.1	46 ± 1
	4-Cl	1.77 ± 0.01	2.89 ± 0.01	4.35 ± 0.03	9.0 ± 0.3	48 ± 1
4-Cl	4-MeO	67.3 ± 0.5	105 ± 1	155 ± 1	8.2 ± 0.3	43 ± 1
	H	7.68 ± 0.02	12.1 ± 0.1	19.9 ± 0.3	9.5 ± 0.4	43 ± 1
	4-Cl	2.16 ± 0.01	3.79 ± 0.01	5.98 ± 0.01	10.3 ± 0.5	43 ± 1

[a]Calculated by Eyring equation.

Table 8. Second-Order Rate Constants ($k_H/M^{-1} s^{-1}$) and Activation Parameters[a] for the Reactions of **10** with $C_6H_5NH_2$ in MeCN

Y	$k_H \times 10^4/M^{-1} s^{-1}$			$\Delta H^{\neq}/$ kcal mol^{-1}	$-\Delta S^{\neq}/$ cal mol^{-1} K^{-1}
	45.0 °C	55.0 °C	65.0 °C		
4-MeO	1.16 ± 0.01	1.55 ± 0.01	2.08 ± 0.01	5.6 ± 0.2	59 ± 1
4-Me	1.31 ± 0.01	1.80 ± 0.01	2.40 ± 0.01	5.8 ± 0.1	58 ± 1
H	1.53 ± 0.01	2.04 ± 0.01	2.79 ± 0.01	5.8 ± 0.3	58 ± 1
3-MeO	1.89 ± 0.01	2.63 ± 0.01	3.62 ± 0.02	6.3 ± 0.1	56 ± 1
4-Cl	2.93 ± 0.01	4.09 ± 0.01	5.66 ± 0.02	6.4 ± 0.1	55 ± 1

[a]Calculated by Eyring equation.

between: $(k_H/k_D)_{min}$ and (i) X; (ii) Y; (iii) anilinolysis mechanism as mentioned earlier.

Tables 7 and 8 list the activation parameters, enthalpies and entropies of activation, for the anilinolyses of **8** and **10**, respectively.[13] The enthalpies of activation are relatively low (5–11 kcal mol^{-1}) and the entropies of activation are relatively large negative values (–39 to –59 cal mol^{-1} K^{-1}) for the anilinolyses of **1-11** as seen in Table R2.[14] The relatively low activation enthalpy and large negative activation entropy are typical for the aminolyses of the P=S (and P=S) systems.

Experimental Section

Materials. Substrates of **8** and **10** were prepared as reported earlier.[15]

Kinetic Procedure. The second-order rate constants and selectivity parameters were obtained as previously described.[1] Initial concentrations were as follows; [substrate] = 5 × 10^{-3} M and [X-Aniline] = (0.10-0.30) M for both substrates.

Product Analysis. Phenyl methyl and 3-methoxyphenyl propyl chlorothiophosphate were reacted with excess aniline for more than 15 half-lives at 55.0 °C in MeCN. Acetonitrile was evaporated under reduced pressure. The product mixture was treated with ether by a work-up process with dilute HCl and dried over anhydrous MgSO$_4$. The product was isolated through column chromatography (25-30% ethyl acetate/*n*-hexane) and then dried under reduced pressure. The analytical and spectroscopic data of the product gave the following results (supporting information):

(C_6H_5O)(CH_3O)P(=S)NHC$_6$H$_5$. Brown gummy solid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 3.79-3.83 (d, 3H), 6.67 (d, br, 1H, *J* = 8.8 Hz), 6.79-6.90 (d, 1H), 7.02-7.09 (t, 1H), 7.15-7.25 (m, 4H) 7.26-7.45 (m, 4H); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 54.26, 115.97, 118.17, 119.56, 121.89, 123.4, 126.2, 130.19, 130.9; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 74.36 (P=S, 1P, d, *J* = 13.9 Hz); GC-MS (EI, *m/z*) 279 (M$^+$).

(3-CH_3O-C_6H_4O)(C_3H_7O)P(=S)NHC$_6$H$_5$. Brown liquid; ^{1}H-NMR (400 MHz, CDCl$_3$ and TMS) δ 1.19-1.26 (m, 3H), 1.74-1.76 (q, 2H), 3.71 (s, 3H), 4.04-4.24 (m, 2H), 5.56 (br. d, *J* = 3.8 Hz, 1H), 6.70-6.77 (m, 2H), 7.02 (t, 4H), 7.08 (d, 4H), 7.18 (t, 1H), 7.27-7.29 (m, 2H); ^{13}C-NMR (100 MHz, CDCl$_3$ and TMS) δ 10.2, 23.3, 55.3, 69.4, 107.3, 111.3, 113.5, 118.0, 122.5, 129.4, 129.8, 139.2, 151.4, 160.4; ^{31}P-NMR (162 MHz, CDCl$_3$ and TMS) δ 66.9 (1P, P=S); GC-MS (EI, *m/z*) 337 (M$^+$).

References and Notes

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3. '$\Sigma E_S = E_S(R_1) + E_S(R_2)$' is employed instead of '$\Sigma E_S = E_S(R_1O) + E_S(R_2O)$' because the data of $E_S(R_iO)$ is not available [$E_S(R) = 0(Me); -0.07(Et); -0.36(Pr); -0.39(Bu); -0.47(i\text{-}Pr); -2.48(Ph)$].

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5. The substrate of **12** is excluded to consider the steric effects of the two ligands on the rate. The anilinolysis rate of **12** (with Y = H) is faster than that of **11** (with Y = H) due to an electron-withdrawing ability of the 4-chloro substituent, although the steric effects of the two ligands of **12** would be slightly greater than those of **11** in the TS.

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7. The correlation coefficients of the sensitivity coefficients (δ) of r = 0.948 with *a* group and r = 0.803 with *b* group indicate relatively poor linear correlation between the steric effects and rate. However, the tendency of the linearity between them could be acceptable *i.e.*, 'not quantitatively but qualitatively' in Figure 2. The problem is that there is no other way to rationalize the steric effects of the two ligands on the rate except Taft eq.

8. As mentioned earlier, the authors suggest that the degrees of both bond formation and cleavage with **10** are greater than those with **8** in the TS based on the magnitudes of the selectivity parameters, $\beta_{X(H)}$, $\rho_{X(H)}$ and $\rho_{Y(H)}$. The CICs have the advantage of the indication of the degree of tightness of the TS structure based on the interaction between the two substituents.

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12. **Table R1.** $(k_H/k_D)_{min}$ of Six Substrates where $(k_H/k_D)_{min} < 0.62$

substrate	$(k_H/k_D)_{min}$	X	Y	ref.
$(Me)(YC_6H_4O)P(=S)Cl$	0.37	4-Cl	4-CN	9a
$(Me_2N)(YC_6H_4O)P(=O)Cl$	0.42	3-Cl	4-MeO	a
$(Ph)(YC_6H_4O)P(=S)Cl$	0.44	4-MeO	4-MeO	b
$(PhO)(PhNH)P(=O)Cl$	0.52	3-Cl	-	c
$[C_2H_2NOC(=O)]_2P(=O)Cl$	0.61	3-Cl	-	d
$(PhO)(YC_6H_4O)P(=O)Cl$	0.61	4-Cl	4-Cl	6a

(a) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2014**, *35*, 753. (b) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3505. (c) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 3437. (d) Barai, H. R.; Lee, H. W. *Bull. Korean Chem. Soc.* **2013**, *34*, 3218.

13. The activation parameters were obtained extensively to find the consistent trends with X and/or Y, however, there is no correlation between the activation parameters and substituents. Moreover, the activation enthalpy-entropy compensation phenomena do not exist.

14. **Table R2.** Activation Parameters for the Reactions of **1-11** with $C_6H_5NH_2$ in MeCN

substrate	$\Delta H^{\ddagger}/$ kcal mol^{-1}	$-\Delta S^{\ddagger}/$ cal mol^{-1} K^{-1}	ref.
1: $(MeO)_2P(=S)Cl$	8.0	49	1a
2: $(MeO)(EtO)P(=S)Cl$	11.2	39	1b
3: $(EtO)_2P(=S)Cl$	6.0	55	1a
4: $(EtO)(PrO)P(=S)Cl$	7.3	52	1b
5: $(PrO)_2P(=S)Cl$	7.3	53	1c
6: $(BuO)_2P(=S)Cl$	7.4	52	1d
7: $(i\text{-}PrO)_2P(=S)Cl$	9.4	47	1b
8: $(MeO)(PhO)P(=S)Cl$	9.8	43	present work
9: $(EtO)(PhO)P(=S)Cl$	5.4	59	1e
10: $(PrO)(PhO)P(=S)Cl$	5.8	58	present work
11: $(PhO)_2P(=S)Cl$	7.7	54	1f

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