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PAPER

Kinetics and mechanism of the anilinolyses of aryl dimethyl, methyl phenyl and diphenyl phosphinates†

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The reactions of Z-aryl dimethyl (**1**), methyl phenyl (**2**), and diphenyl (**3**) phosphinates with X-anilines in dimethyl sulfoxide at 60.0 °C are studied kinetically. Kinetic results yield the primary normal deuterium kinetic isotope effects (DKIEs) involving deuterated aniline ($XC_6H_4ND_2$) nucleophiles, $k_H/k_D = 1.03–1.17$, 1.15–1.29, and 1.24–1.51, and the cross-interaction constants (CICs), $\rho_{XZ} = 0.37$, 0.34, and 0.65 for **1**, **2**, and **3**, respectively. The steric effects of the ligands (R_1 and R_2) on reaction rates play a role, but are relatively much smaller compared to other phosphinate systems. A stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate is proposed on the basis of the CICs positive signs. The dominant frontside nucleophilic attack through a hydrogen-bonded, four-center-type transition state is proposed on the basis of primary normal DKIEs and large magnitudes of the CICs for **2** and **3**, while both frontside and backside attack are proposed on the basis of relatively small primary normal DKIEs for **1**.

Introduction

Phosphoryl transfers from phosphates and thiophosphates are an important class of reaction and a considerable amount of work has been carried out towards mechanism elucidation. Nucleophilic displacement reactions of tetracoordinated phosphorus have been studied for a variety of substrates containing the phenoxide leaving group.[1–5] Two main types of displacement processes are well known in neutral phosphoryl and thiophosphoryl group transfer reactions: the stepwise mechanism involving a trigonal bipyramidal pentacoordinate (TBP-5C) intermediate; concerted displacement at the phosphorus through a single pentacoordinate transition state (TS).

In previous work, this lab reported various phosphoryl and thiophosphoryl transfer reactions.[6] Continuing the studies of the anilinolyses of phosphinates, kinetic studies of the reactions of Z-aryl dimethyl (**1**), methyl phenyl (**2**), and diphenyl (**3**) phosphinates, containing the Z-substituted phenoxide leaving group, with X-anilines have been carried out in DMSO at 60.0 °C, eqn (1), to clarify the anilinolysis mechanism and stereochemistry by comparing the reactivity, the sign and magnitude of the cross-interaction constants (CICs), the steric effects, and finally the deuterium kinetic isotope effects (DKIEs; k_H/k_D) with those obtained in the previous work, especially with the anilinoyses of their phosphinic chloride counterparts, dimethyl [$Me_2P(=O)Cl$; **1′**],[6i] methyl phenyl [$MePhP(=O)Cl$; **2′**],[6i] and diphenyl [$Ph_2P(=O)Cl$; **3′**][6d] phosphinic chlorides.

$$R_1R_2P(=O)OC_6H_4Z + 2NL_2C_6H_4X \xrightarrow[60.0\ ^{\circ}C]{DMSO} R_1R_2P(=O)NLC_6H_4X + XC_6H_4\overset{+}{N}L_3OC_6H_4\overset{-}{Z}$$

1: $R_1 = R_2 = Me$; **2:** $R_1 = Me$, $R_2 = Ph$; **3:** $R_1 = R_2 = Ph$
L = H (or D) when Z = 4-NO_2
X = 4-MeO, 4-Me, 3-Me, H, 3-MeO, 4-Cl, and 3-Cl
Z = 4-MeO, H, and 4-NO_2

(1)

Results and discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obeyed eqn (2) with a negligible k_0 (= 0) in DMSO. The reactions were carried out under pseudo-first-order conditions with a large excess of the aniline nucleophile.

$$k_{obsd} = k_0 + k_{H(D)}[XC_6H_4NH_2(D_2)] \qquad (2)$$

Linear plots of eqn (2) suggest a lack of base-catalysis or noticeable side reactions and that the overall reactions follow the route given by eqn (1). The second-order rate constants (k_H and k_D) for the reactions of **1**, **2**, and **3** with X-anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) in DMSO at 60.0 °C are summarized in Tables 1–3 together with selectivity parameters (ρ_X, β_X, ρ_Z, β_Z, and ρ_{XZ}). The rate increases with a more electron-withdrawing substituent Z in the leaving group and a more electron-donating substituent X in the nucleophile, which is consistent with a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom ($\rho_X < 0$) and negative charge development at the phenoxy oxygen atom ($\rho_Z > 0$) in the TS.

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Table 1 Second-order rate constants ($k_{H(D)} \times 10^4$/M^{-1} s^{-1}) and selectivity parameters[a] (ρ_X, β_X, ρ_Z, β_Z, and ρ_{XZ}) of the aminolysis of $Me_2P(=O)OC_6H_4Z$ (**1**) with $XC_6H_4NH_2(D_2)$ in DMSO at 60.0 °C

X / Z		4-Me	H	4-NO$_2$	$\rho_{Z(H)}$	$-\beta_{Z(H)}$	
4-MeO	k_H	2.06 ± 0.06[b]	2.72 ± 0.05	6.06 ± 0.12	0.48 ± 0.03	0.06 ± 0.01[c]	0.14 ± 0.03[d]
	k_D			5.17 ± 0.15			
4-Me	k_H			5.20 ± 0.14			
	k_D			4.48 ± 0.12			
3-Me	k_H			4.72 ± 0.11			
	k_D			4.10 ± 0.11			
H	k_H	1.03 ± 0.02	1.52 ± 0.04	4.06 ± 0.08	0.60 ± 0.06	0.07 ± 0.01	0.18 ± 0.04
	k_D			3.67 ± 0.09			
3-MeO	k_H			3.63 ± 0.03			
	k_D			3.35 ± 0.05			
4-Cl	k_H			3.23 ± 0.09			
	k_D			3.05 ± 0.11			
3-Cl	k_H	0.538 ± 0.013	0.845 ± 0.02	2.74 ± 0.05	0.72 ± 0.07	0.09 ± 0.01	0.21 ± 0.04
	k_D			2.66 ± 0.07			
$-\rho_{X(H)}$[e]		0.90 ± 0.09	0.79 ± 0.07	0.53 ± 0.02	$\rho_{XZ(H)}$ = 0.37 ± 0.13		
$-\rho_{X(D)}$[e]				0.44 ± 0.02			
$\beta_{X(H)}$		0.32 ± 0.04	0.28 ± 0.04	0.19 ± 0.01			
$\beta_{X(D)}$				0.16 ± 0.01			

[a] The σ and pK_a values of the X-anilinium ions in water were taken from ref. 9 and 10, respectively. [b] Standard deviation. [c] Calculated from the pK_a values of Z-phenols in DMSO. [d] Calculated from the pK_a values of Z-phenols in water. [e] The subscripts (H) and (D) indicate that the values are calculated from k_H and k_D, respectively.

Table 2 Second-order rate constants ($k_{H(D)} \times 10^4$/M^{-1} s^{-1}) and selectivity parameters[a] (ρ_X, β_X, ρ_Z, β_Z, and ρ_{XZ}) of the aminolysis of $MePhP(=O)OC_6H_4Z$ (**2**) with $XC_6H_4NH_2(D_2)$ in DMSO at 60.0 °C

X \ Z		4-Me	H	4-NO$_2$	$\rho_{Z(H)}$	$-\beta_{Z(H)}$	
4-MeO	k_H	1.52 ± 0.06[b]	2.20 ± 0.02	5.84 ± 0.03	0.59 ± 0.06	0.07 ± 0.01[c]	0.17 ± 0.04[d]
	k_D			4.52 ± 0.13			
4-Me	k_H			5.16 ± 0.05			
	k_D			4.07 ± 0.13			
3-Me	k_H			3.90 ± 0.11			
	k_D			3.12 ± 0.09			
H	k_H	0.648 ± 0.020	1.00 ± 0.01	3.37 ± 0.01	0.73 ± 0.06	0.09 ± 0.01	0.22 ± 0.04
	k_D			2.77 ± 0.06			
3-MeO	k_H			2.87 ± 0.07			
	k_D			2.39 ± 0.07			
4-Cl	k_H			2.31 ± 0.02			
	k_D			1.97 ± 0.05			
3-Cl	k_H	0.303 ± 0.007	0.471 ± 0.015	1.88 ± 0.04	0.81 ± 0.05	0.10 ± 0.01	0.24 ± 0.04
	k_D			1.63 ± 0.06			
$-\rho_{X(H)}$[e]		1.08 ± 0.13	1.04 ± 0.11	0.79 ± 0.03	$\rho_{XZ(H)}$ = 0.34 ± 0.15		
$-\rho_{X(D)}$[e]				0.71 ± 0.03			
$\beta_{X(H)}$		0.38 ± 0.05	0.36 ± 0.04	0.28 ± 0.01			
$\beta_{X(D)}$				0.25 ± 0.01			

[a] The σ and pK_a values of the X-anilinium ions in water were taken from ref. 9 and 10, respectively. [b] Standard deviation. [c] Calculated from the pK_a values of Z-phenols in DMSO. [d] Calculated from the pK_a values of Z-phenols in water. [e] The subscripts (H) and (D) indicate that the values are calculated from k_H and k_D, respectively.

The β_Z (= β_{lg}) values listed in Tables 1–3 are determined using the pK_a values in DMSO and water. Correlations between pK_a values in water[7] and those in DMSO[8] of sixteen substituted phenols with r = 0.972 (eqn (3)) follow:

$$pK_a\ (H_2O) = (0.39 \pm 0.03)pK_a\ (DMSO) + 2.92 \pm 0.40 \qquad (3)$$

Thus, the β_Z values determined using the pK_a values in DMSO are smaller than those using the pK_a values in water, as seen in Tables 1–3. The β_X (= β_{nuc}) values listed in Tables 1–3 seem to be less reliable since the pK_a values used are not those determined in DMSO, but rather water. Using the pK_a values for the anilinium ions determined in DMSO, an approximate straight line is obtained when they are plotted against those determined in water.[11] Spillane and co-workers reported that the β_X value for the reactions of *N*-phenyl sulfamoyl chloride ($PhNHSO_2Cl$) with X-anilines in DMSO is similar when determined using the pK_a values of anilines measured in water ($\beta_X = 0.69$) and DMSO ($\beta_X = 0.62$).[12] Accordingly, it may be inferred that the β_X values in Tables 1–3 are reasonably positive. The pK_a and σ values of deuterated anilines are assumed to be the same as those of anilines.

As shown in Fig. 1, the natural bond order (NBO) charges of the P atom reaction center with Z = 4-NO$_2$ [2.072 (**1**), 2.096 (**2**), and 2.117 (**3**)][6f] are consistent with expectations for the electronic influence of the ligands [$\Sigma\sigma_I$ = −0.02 (Me$_2$), 0.11 (MePh), and

Table 3 Second-order rate constants ($k_{H(D)} \times 10^4/M^{-1}\ s^{-1}$) and selectivity parameters[a] (ρ_X, β_X, ρ_Z, β_Z, and ρ_{XZ}) of the aminolysis of $Ph_2P({=}O)OC_6H_4Z$ (**3**) with $XC_6H_4NH_2(D_2)$ in DMSO at 60.0 °C

X \ Z		4-Me	H	4-NO$_2$	$\rho_{Z(H)}$	$-\beta_{Z(H)}$	
4-MeO	k_H	1.42 ± 0.04[b]	2.09 ± 0.06	5.74 ± 0.17	0.62 ± 0.06	0.07 ± 0.01[c]	0.18 ± 0.04[d]
	k_D			3.79 ± 0.12			
4-Me	k_H			5.08 ± 0.08			
	k_D			3.39 ± 0.06			
3-Me	k_H			3.79 ± 0.09			
	k_D			2.74 ± 0.06			
H	k_H	0.466 ± 0.009	0.815 ± 0.024	3.19 ± 0.09	0.84 ± 0.09	0.10 ± 0.02	0.25 ± 0.05
	k_D			2.37 ± 0.07			
3-MeO	k_H			2.76 ± 0.08			
	k_D			2.07 ± 0.06			
4-Cl	k_H			2.20 ± 0.04			
	k_D			1.76 ± 0.05			
3-Cl	k_H	0.163 ± 0.004	0.331 ± 0.009	1.74 ± 0.04	1.03 ± 0.13	0.12 ± 0.02	0.30 ± 0.07
	k_D			1.41 ± 0.04			
$-\rho_{X(H)}$[e]		1.45 ± 0.16	1.24 ± 0.13	0.83 ± 0.04	$\rho_{XZ(H)} = 0.65 \pm 0.22$		
$-\rho_{X(D)}$[e]				0.68 ± 0.02			
$\beta_{X(H)}$		0.51 ± 0.06	0.43 ± 0.05	0.29 ± 0.01			
$\beta_{X(D)}$				0.24 ± 0.01			

[a] The σ and pK_a values of the X-anilinium ions in water were taken from ref. 9 and 10, respectively. [b] Standard deviation. [c] Calculated from the pK_a values of Z-phenols in DMSO. [d] Calculated from the pK_a values of Z-phenols in water. [e] The subscripts (H) and (D) indicate that the values are calculated from k_H and k_D, respectively.

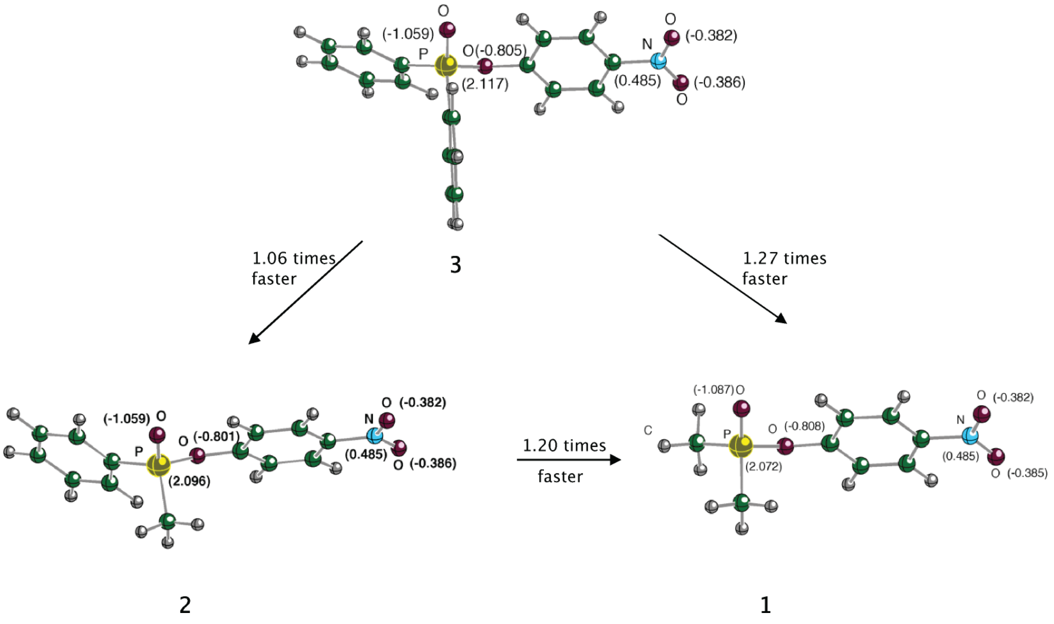


Fig. 1 The B3LYP/6-311+G(d,p) geometries and the NBO charges of **1**, **2**, and **3** with Z = 4-NO$_2$ in the gas phase.[6f] The anilinolysis ($C_6H_5NH_2$) rate ratios in DMSO at 60.0 °C are displayed next to the arrows.

0.24 (Ph$_2$) with σ_I = 0.12 (Ph) and −0.01 (Me)].[13] The plot of $\Sigma\sigma_I$ of the two ligands against the NBO charges on the P atom of three phosphinates gives a slope of 5.77 with a correlation coefficient r = 0.999. However, the second-order rate constants for the anilinolyses of the three phosphinates (**1**, **2**, and **3** with Z = 4-NO$_2$) give relative rates of 1.27 (k_H = 4.06): 1.06 (k_H = 3.37): 1 ($k_H = 3.19 \times 10^{-4}\ M^{-1}\ s^{-1}$) in DMSO at 60.0 °C, contrary to expectations for the electronic influence of the ligands.

The second-order rate constants (k_H) for the anilinolyses (unsubstituted aniline; $C_6H_5NH_2$) of the three phosphinic chlorides [$Me_2P({=}O)Cl$ (**1′**), $MePhP({=}O)Cl$ (**2′**), and $Ph_2P({=}O)Cl$ (**3′**)] gave relative rates of 4520 (k_H = 7.82)[6i,14]: 80 (k_H = 0.138)[6i]: 1 (k_H = 0.00173 $M^{-1}\ s^{-1}$)[6d] in MeCN at 55.0 °C. A plot of log k_H against the Taft's steric constants, according to eqn (4), for the anilinolyses of the three phosphinic chlorides gave the sensitivity coefficient of the steric effects, δ = 0.737 (r = 0.999; incidentally good linearity), where $\sum E_S$ is the sum of the Taft's steric constants [$\sum E_S$ = 0.00 (Me$_2$), −2.48 (MePh), and −4.96 (Ph$_2$) with E_S = 0.00 (Me) and −2.48 (Ph)].[15]

$$\log k = \delta \Sigma E_S + C \qquad (4)$$

Buncel and co-workers reported that the second-order rate constants for the ethanolyses of the three phosphinates (**1**, **2**, and **3** with Z = 4-NO$_2$) gave relative rates of 235 (k_{EtO^-} = 230):

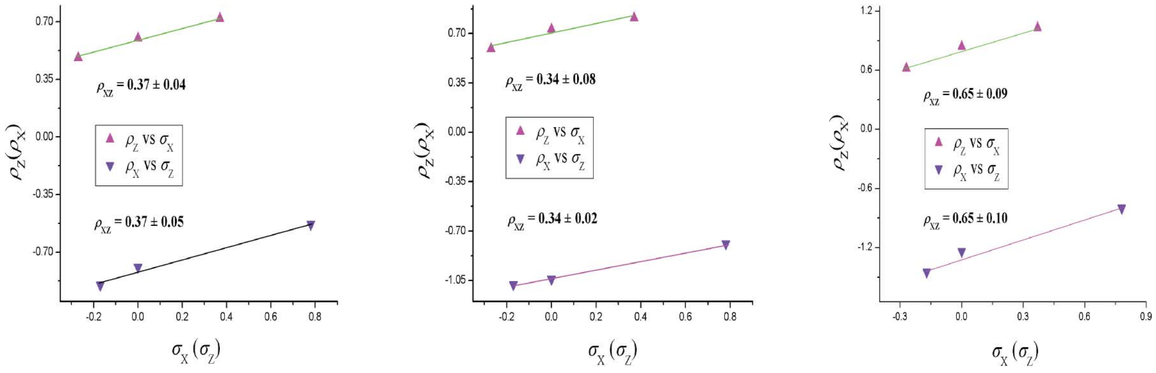


Fig. 2 Determination of ρ_{XZ} (= $\partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X$) by plotting ρ_Z (or ρ_X) against σ_X (or σ_Z) according to eqn (5b) for the reactions of **1**, **2**, and **3** with $XC_6H_4NH_2$ in DMSO at 60.0 °C. The values obtained by multiple regressions are: ρ_{XZ} (**1**) = 0.37 ± 0.13 (r = 0.995); ρ_{XZ} (**2**) = 0.34 ± 0.15 (r = 0.995); ρ_{XZ} (**3**) = 0.65 ± 0.22 (r = 0.993).

69 (k_{EtO^-} = 67.6): 1 (k_{EtO^-} = 0.980 M^{-1} s^{-1}) in anhydrous ethanol at 25.0 °C, resulting in δ = 0.478 (r = 0.953) when the same values of $\sum E_S$ as in the anilinolysis of the three phosphinic chlorides, were used.[5b,c,i,j] Williams and co-workers reported that the second-order rate constants for the phosphate catalyzed hydrolyses of two phosphinates (**1** and **3** with Z = 4-NO$_2$) gave a relative rate of 52 ($k_{HPO_4{}^{2-}}$ = 1.06 × 10^{-2}): 1 ($k_{HPO_4{}^{2-}}$ = 2.05 × 10^{-4} M^{-1} s^{-1}) in 10% dioxane–aqueous 0.1 M NaCl at 25.0 °C, resulting in δ = 0.345.[3a,b] These results suggested that the relative reactivities of the phosphinates are predominantly dependent on steric effects over the inductive effects of the ligands.

However, a plot of log k_H for the anilinolyses ($C_6H_5NH_2$) of **1**, **2**, and **3** with Z = 4-NO$_2$ in DMSO at 60.0 °C against the summation of Taft's steric constants according to eqn (4) gives a considerably small value of δ = 0.021 (r = 0.954) compared to earlier results: δ = 0.737 for the anilinolyses of three phosphinic chlorides; 0.478 for the ethanolyses of three phosphinates; 0.345 for the hydrolyses of two phosphinates. It is evident that the steric effects (the two ligands: R$_1$ and R$_2$) upon the anilinolysis rates of the present work do play a role over the inductive effects of the ligands, but rather a much smaller steric effect compared to the anilinolyses of three phosphinic chlorides, the ethanolyses of three phosphinates, and the hydrolyses of two phosphinates (35, 23, and 16 times smaller, respectively).

The cross-interaction constants (CICs), ρ_{XZ}, eqn (5), are determined, where X and Z represent the substituents in the nucleophile and leaving group, respectively.[16]

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (5a)$$

$$\rho_{XZ} = \partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X \quad (5b)$$

The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and the degree of tightness of the TS, respectively. In general, the ρ_{XZ} has a negative value (or sometimes a small positive value) in a concerted S$_N$2 reaction and a stepwise reaction with a rate-limiting bond formation. In contrast, it has a positive value for a stepwise reaction with a rate-limiting leaving group departure from the intermediate.[16] The magnitude of ρ_{XZ} is inversely proportional to the distance between the nucleophile and leaving group in the TS.[16]

Fig. 2 shows the plots of ρ_Z *vs* σ_X and ρ_X *vs* σ_Z for the anilinolyses ($XC_6H_4NH_2$) of **1**, **2**, and **3** in DMSO at 60.0 °C.[17] The positive ρ_{XZ} values (ρ_{XZ} = +0.37, +0.34, and +0.65 for **1**, **2**, and **3**, respectively) indicate that the studied reactions proceed through a stepwise mechanism with a rate-limiting leaving group departure from the intermediate, eqn (6).[16]

$$\text{Substrate} + \text{Nucleophile} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{Intermediate} \xrightarrow{k_b} \text{Products} \quad (6)$$

The β_X (= β_{nuc}) values of anilines are greater than those of deuterated anilines, while the magnitudes are in the range of 0.19–0.29 for anilines and 0.16–0.25 for deuterated anilines. These values seem to be small for a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate and demonstrates that the magnitudes of β_X (and ρ_X) alone cannot provide conclusive evidence of the reaction mechanism.

The magnitudes of the ρ_{XZ} values in the present work are somewhat greater than those of normal bimolecular nucleophilic substitution reactions.[18] Especially in the anilinolysis of **3** bearing two large phenyl ligands, the relatively large magnitude of CIC, ρ_{XZ} = +0.65, strongly implies that the nucleophile and leaving group are in close enough proximity to strongly interact, such as the TS involving a frontside nucleophilic attack.[18] The large magnitudes of the ρ_{XZ} values ($|\rho_{XZ}| > 0.4$) were obtained, given the frontside nucleophilic attack as follows: (i) ρ_{XZ} = −1.98 for the reactions of Z-aryl bis(4-methoxyphenyl) phosphates with weakly basic pyridines in MeCN;[6b] (ii) ρ_{XZ} = −1.70 for the anilinolysis of anilino thioethers in MeOH;[19a] (iii) ρ_{XZ} = −0.50 for the anilinolysis of both Z-substituted 2- and 3-thiopheneethyl arenesulfonates in MeCN;[19b] (iv) ρ_{XZ} = −0.75 for the anilinolysis of Z-substituted cumyl arenesulfonates in MeCN;[19c] (v) ρ_{XZ} = −0.56 for the anilinolysis of Z-substituted 1-phenylethyl arenesulfonates in MeOH;[19d] (vi) ρ_{XZ} = −0.45 for the anilinolysis of *Z*-substituted 2-phenylethyl arenesulfonates in MeOH;[19e] (vii) ρ_{XZ} = +1.06 for the benzylaminolysis of *Z*-aryl cyclopropanecarboxylates in MeCN;[19f] (viii) ρ_{XZ} = +1.19 for the benzylaminolysis of Z-aryl 2-furoates in MeCN;[19g] (ix) ρ_{XZ} = +0.90 for the benzylaminolysis of Z-thiophenyl acetates in MeCN.[19h] In the anilinolyses of **1** and **2**, the ρ_{XZ} values of ~0.35 (0.37 and 0.34, respectively) imply the possibility of a partial participation of frontside nucleophilic attack (*vide infra*).

The DKIEs (k_H/k_D) for the reactions of **1**, **2**, and **3** with Z = 4-NO$_2$ involving deuterated anilines ($XC_6H_4ND_2$) in DMSO at 60.0 °C are summarized in Table 4. The observed DKIEs are all

Table 4 Deuterium kinetic isotope effects (k_H/k_D) for the reactions of **1**, **2**, and **3** (when Z = 4-NO_2) with $XC_6H_4NH_2(D_2)$ in DMSO at 60.0 °C

X \ substrate	**1**	**2**	**3**
4-MeO	1.17 ± 0.01[a]	1.29 ± 0.01	1.51 ± 0.01
4-Me	1.16 ± 0.01	1.27 ± 0.01	1.50 ± 0.01
3-Me	1.15 ± 0.01	1.25 ± 0.01	1.38 ± 0.01
H	1.11 ± 0.01	1.22 ± 0.01	1.35 ± 0.02
3-MeO	1.08 ± 0.01	1.20 ± 0.01	1.33 ± 0.02
4-Cl	1.06 ± 0.01	1.17 ± 0.02	1.25 ± 0.02
3-Cl	1.03 ± 0.01	1.15 ± 0.03	1.23 ± 0.02

[a] Standard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ from ref. 20

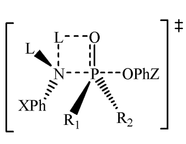
Table 5 Comparison of the DKIEs (k_H/k_D) of the anilinolyses of **1**, **2**, and **3** (when $Z = 4\text{-}NO_2$) in DMSO at 60.0 °C with those of their phosphinic chloride counterparts (**1′**, **2′**, and **3′**) in MeCN

Substrate	k_H/k_D	Substrate	k_H/k_D
1: $Me_2P(=O)OC_6H_4$-4-NO_2	1.03–1.17	**1′**: $Me_2P(=O)Cl$[a]	0.703–0.899[c]
2: $MePhP(=O)OC_6H_4$-4-NO_2	1.15–1.29	**2′**: $MePhP(=O)Cl$[a]	1.62–2.10[d]
3: $Ph_2P(=O)OC_6H_4$-4-NO_2	1.23–1.51	**3′**: $Ph_2P(=O)Cl$[b]	1.42–1.82[d]

[a] Ref. 6i. [b] Ref. 6d. [c] Values at 15.0 °C. [d] At 55.0 °C.

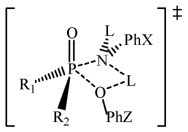
greater than unity, $k_H/k_D > 1$. The magnitudes of the DKIEs gradually decrease from 1.23–1.51 (**3**) *via* 1.15–1.29 (**2**) to 1.03–1.17 (**1**) as the size of the two ligands (R_1 and R_2) decreases from diphenyl (**3**) *via* methyl phenyl (**2**) to dimethyl (**1**), and a stronger nucleophile leads to a greater DKIE.

In the present work, the overall second-order rate constant is given by $k_{H(D)} = (k_a/k_{-a})k_b = Kk_b$ (eqn (6)) in which the breakdown of the intermediate is the rate-limiting. Since the equilibrium step (K) results in an almost negligible DKIE due to cancellation of the k_a and k_{-a} terms, the observed k_H/k_D mainly reflects the leaving group expulsion rate constant (k_b) from the intermediate.[21] The primary normal DKIEs ($k_H/k_D > 1$) suggest that partial deprotonation of the aniline occurs in the rate-determining step by hydrogen bonding, while the secondary inverse DKIEs ($k_H/k_D < 1$) imply an increase in the N–H(D) vibrational frequencies as a result of steric congestion of the N–H(D) moiety in the TS.[6a–k,22] Regarding the observed primary normal DKIEs, the TS I could be one of the plausible structures where the hydrogen bond forms between the hydrogen (or deuterium) atom in the N–H(D) moiety and the oxygen atom in P=O. Herein, both the nucleophile and leaving group occupy apical positions in a TBP-5C TS due to a backside nucleophilic attack. When the studied reactions proceed through the TS I, the sequence of the magnitudes of the primary normal DKIEs should be **1** > **2** > **3** since the sequence of the steric congestion due to the two ligands is **3** > **2** > **1**, and the sequence of the magnitude of the negative charge on the oxygen atom of P=O is −1.087 (**1**) > −1.059 (**2**) ≈ −1.059 (**3**) (see Fig. 1). The obtained sequence of the DKIEs (**3** > **2** > **1**) is completely contrary to expectations from both the steric congestion of the two ligands and negative charge on the oxygen atom. Thus, the TS I can be safely ruled out to substantiate the observed primary normal DKIEs.



TS I

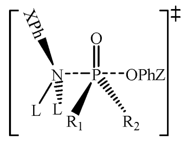
To rationalize the primary normal DKIEs, the TS II involving a frontside nucleophilic attack is proposed as a most plausible structure, in which the nucleophile and leaving group are located adjacent to each other in order to form the hydrogen bond between the hydrogen (or deuterium) atom in the N–H(D) moiety and the oxygen atom in the leaving group. The participation of a hydrogen bonded, four-center-type TS II-like was reported for the benzylaminolyses of aryl cyclopropanecarboxylates,[19f] ethyl aryl carbonates,[23] and aryl cyclobutanecarboxylates[24] with the phenoxide leaving group in MeCN on the basis of the primary normal DKIEs involving deuterated benzylamine ($XC_6H_4CH_2ND_2$), k_H/k_D = 1.21–1.48, 1.56–1.78, and 1.19–1.46, respectively. A partial participation of a hydrogen-bonded, four-center-type TS II-like in a frontside nucleophile attack was proposed on the basis of k_H/k_D = 1.70–2.35 of the anilinolysis of 1-phenyl ethyl benzenesulfonates in MeOH–MeCN.[25] Moreover, a participation of a four-center-type TS II-like, involving a hydrogen bond between the hydrogen (or deuterium) atom in the N–H(D) moiety and the leaving group Cl, was proposed for the anilinolyses of R_1R_2P(=O or S)Cl-type substrates in MeCN on the basis of the primary normal DKIEs.[6c–k]



TS II

In the case of the anilinolyses of phosphinic chlorides where the reactions proceed through a concerted mechanism, the k_H/k_D values of **1′**[6i] are secondary inverse (k_H/k_D = 0.703–0.899), while those of **2′**[6i] and **3′**[6d] are primary normal (k_H/k_D = 1.62–2.10 and 1.42–1.82, respectively), as seen in Table 5. These results were substantiated by the steric effect of the two ligands: (i) in **1′**, where the two small ligands (Me_2) readily enable dominant backside attack of the aniline nucleophile, resulting in large secondary inverse DKIEs; (ii) in **2′**, where backside nucleophilic attack is forbidden due to one small (Me) and one large (Ph) ligand, and a predominant frontside attack, involving hydrogen-bonded, four-center-type TS II-like, is favorable, resulting in the great primary normal DKIEs;[26] (iii) in **3′**, where two large ligands (Ph_2) lead to the same result as in **2′**.[26]

Comparing the DKIEs of the present work with those of phosphinic chloride counterparts, the DKIEs of **2**, **2′**, **3**, and **3′** are evidently primary normal, although the DKIEs of **2** with Z = 4-NO_2 are considerably smaller than those of **2′**, and those of **3** with Z = 4-NO_2 are slightly smaller than those of **3′**. However, the small primary normal DKIEs of **1** with Z = 4-NO_2 are obtained in contrast to the large secondary inverse DKIEs of **1′**. These results can be rationalized as follows (*vide supra*): (i) in **1**, both frontside ($k_H/k_D > 1$; TS II) and backside ($k_H/k_D < 1$; TS III) attacks yield small magnitudes of the primary normal DKIEs, k_H/k_D = 1.03–1.17; (ii) in **2**, a great fraction of the frontside attack with a small fraction of backside attack yields medium magnitudes (mean values of **1** and **3**) of the primary normal DKIEs, k_H/k_D = 1.15–1.29; (iii) in **3**, predominant frontside attack (consistent with the prediction from the large magnitude of ρ_{XZ} = +0.65) yields large magnitudes of the primary normal DKIEs, k_H/k_D = 1.23–1.51.



TS III

The second-order rate constants of the anilinolyses (with unsubstituted aniline: $C_6H_5NH_2$) of **1′** in MeCN at 15.0 °C[6i] and **1** with Z = H in DMSO at 60.0 °C are $k_H = 1.61 \times 10^0$ and 1.52×10^{-4} M^{-1} s^{-1} ($k_H = 1.03 \times 10^{-4}$ when Z = Me and 4.06×10^{-4} M^{-1} s^{-1} when Z = 4-NO_2), respectively. Taking into account the differences in solvent polarity and reaction temperature between the two reactions; MeCN (dielectric constant: ε_r = 35.94) *vs.* DMSO (ε_r = 46.45) and 15.0 *vs.* 60.0 °C, respectively, the leaving group mobility of OC_6H_4Z is really very poor compared to Cl. The poor leaving group mobility of OC_6H_4Z introduces the TS II together with TS III in **1**, since the TS II can be stabilized by the hydrogen bond enough to compete with the TS III, in spite of the small steric hindrance of two small Me ligands. However, in **2** and **3**, TS II is more favorable than TS III because of the greater steric hindrance of the two ligands. It needs to be stressed that a frontside nucleophilic attack with a hydrogen bonded, four-center-type TS II could be a possible pathway, even when the steric hindrance of the two ligands is not so great, *especially for the system studied herein with poor leaving group mobility*.

Regarding the steric effects of the two ligands (R_1 and R_2) on the reaction pathways, they work in a different manner: (i) in the present work, the steric congestion of a frontside attack (TS II) should be much smaller than that of a backside attack (TS III). As a result, a considerably small value of δ = 0.021 in eqn (4) is obtained; (ii) a large value of δ = 0.478 was observed for the ethanolyses of the three phosphinates (**1**, **2**, and **3** with Z = 4-NO_2) due to a backside attack (TS III-like);[5b,c,i,j] (iii) a great value of δ = 0.737 for the reactions of the three phosphinic chlorides (**1′**, **2′**, and **3′**) with anilines may raise a question, since the anilinolyses of **2′** and **3′** proceed through TS II-like involving a predominant frontside attack while the anilinolysis of **1′** proceeds through TS III-like involving a dominant backside attack.[6d,i] In general, when the leaving group is a good one, such as chloride, a backside attack is appreciably more favorable than a frontside attack, and the phosphoryl transfer reactions mainly proceed through a backside attack regardless of the reaction mechanism, concerted or stepwise. However, in the case of (iii), a frontside attack (TS II) could be an alternative pathway *competing* with a backside attack because of not only a relatively large size of aniline nucleophile but also the orientation restriction of the attacking aniline when the degree of steric hindrance becomes great. Accordingly, the extensive steric hindrance of the two ligands to a frontside attack reflects the steric hindrance to a backside attack, resulting in a great value of δ = 0.737.

One might guess that the DKIEs of k_H/k_D = 1.03–1.17 for **1** are not the primary normal α-type but rather the secondary normal β-type when the rate-determining step is the breakdown of the intermediate in a stepwise mechanism.[27] However, the values of k_H/k_D = 1.03–1.17 are too large to be the secondary normal β-DKIEs. If the reaction proceeds through a predominant backside nucleophilic attack (TS III), the large secondary inverse DKIEs (k_H/k_D <1) over the small secondary normal β-DKIEs (k_H/k_D = 1.0–1.1)[28] should result in k_H/k_D <1. The large secondary inverse DKIEs of k_H/k_D = 0.703–0.899 due to a backside attack for **1′** can be supporting evidence.[29] Furthermore, the unprecedented great secondary inverse DKIE of k_H/k_D = 0.367 was observed for the anilinolysis (X = 4-CN) of Y-*O*-aryl methyl phosphonochloridothioates (Y = 4-Cl) in MeCN at 55.0 °C, in which the rate-limiting step is leaving group expulsion from the intermediate.[6k,29]

According to the TS II and III, the observed primary normal DKIEs in Table 4 would be the sum of: (i) the primary normal DKIE, k_H/k_D >1, because of the partial deprotonation of one of the two N–H(D) bonds in the TS II for a frontside attack; (ii) the secondary inverse DKIE, k_H/k_D <1, because of the steric hindrance that increases the out-of-plane bending vibrational frequencies of the other N–H(D) bond in TS II for a frontside attack; (iii) the secondary inverse DKIE, k_H/k_D < 1, because of the steric congestion that increases the vibrational frequencies of both of the N–H(D) bonds in TS III for a back-side attack (especially for **1**); (iv) lowering the k_H/k_D value because of the nonlinear and unsymmetrical structure of N $\cdots$ H(D) $\cdots$ O in TS II; (v) lowering the k_H/k_D value because of heavy atom (N and O) contribution to the reaction-coordinate motion.[22] Thus, the real primary normal DKIE due to the hydrogen bond between the hydrogen of the N–H(D) moiety and the phenoxy oxygen of the leaving group should be greater than the observed value.

In summary, a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate is proposed for the reactions of Z-aryl dimethyl (**1**), methyl phenyl (**2**), and diphenyl (**3**) phosphinates with substituted anilines in DMSO at 60.0 °C, based on the positive cross-interaction constants, ρ_{XZ}. The steric effects of the two ligands play a role in determining the reactivity of phosphinates, but are relatively small compared to other phosphinate systems. A dominant frontside nucleophilic attack involving a hydrogen-bonded, four-center-type TS II is proposed in the anilinolysis of **2** and **3**, while both frontside and backside attacks are proposed in the anilinolysis of **1**,[30] based on the magnitudes of the ρ_{XZ} values, the primary normal DKIEs, the degree of steric hindrance, and the kinetic results of their phosphinic chloride counterparts, dimethyl (**1′**), methyl phenyl (**2′**), and diphenyl (**3′**) phosphinic chlorides.

Experimental section

Materials and products

GR-grade dimethyl, methyl phenyl, and diphenyl phosphinic chlorides, and HPLC-grade acetonitrile (water content < 0.005%) were used without further purification for the kinetic studies. Anilines were redistilled or recrystallized before use. Deuterated anilines were prepared by heating the anilines with D_2O and one drop of HCl catalyst at 85 °C for 72 h. After numerous attempts, the anilines were more than 98% deuterated, as confirmed by ^{1}H-NMR analysis. Syntheses of Z-substituted substrates and products with the analytical and spectroscopic data are available in the ESI.†

Kinetic procedure

The second-order rate constants ($k_{H(D)}$) and pseudo-first-order rate constants (k_{obsd}) were determined as previously described[6a–k] with a large excess of anilines: [Aniline] = 0.01–0.13 M; [Substrate] = 0.1–1 × 10^{-3} M.

Acknowledgements

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18 The magnitudes of ρ_{XZ} values for backside nucleophilic attack S_N2 pathways are generally in the range of –0.1 to –0.3, since the nucleophile and leaving group are far apart. The ρ_{XZ} values greater than ~0.4 ($|\rho_{XZ}| > 0.4$) suggest that the reactions proceed predominantly by the frontside nucleophilic attack pathways.

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26 The k_H/k_D = 2.10 of the reaction of **2′** [MePhP(= O)Cl] with 4-methoxy aniline in MeCN at 55.0 °C is the largest one observed for the anilinolyses of R_1R_2P(= O or S)Cl-type substrates. Although the primary normal DKIEs (k_H/k_D = 1.62–2.10) of **2′** are greater than those (k_H/k_D = 1.42–1.82) of **3′** [Ph_2P(= O)Cl], there is no doubt that the anilinolyses of both substrates predominantly proceed through frontside nucleophilic attack. The subtle combination of Me and Ph gives an unexpected result.

27 (*a*) Ref. 22c; ch. 6; (*b*) F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824; (*c*) K. C. Westaway, *Adv. Phys. Org. Chem.*, 2006, **41**, 217.

28 The secondary normal β-type-DKIEs, $k_H/k_D > 1$, involving the rate-limiting leaving group expulsion from the intermediate were obtained: (*a*) k_H/k_D = 1.03–1.11 for the reactions of phenylacetyl chlorides with deuterated anilines in MeCN (H. W. Lee, J. W. Lee, H. J. Koh and I. Lee, *Bull. Korean Chem. Soc.*, 1998, **19**, 642); (*b*) k_H/k_D = 1.04–1.12 for the reactions of 4-nitrophenyl *N*-phenylcarbamates with deuterated benzylamines in MeCN (H. J. Koh, O. S. Kim, H. W. Lee and I. Lee, *J. Phys. Org. Chem.*, 1997, **10**, 725); (*c*) k_H/k_D = 1.02–1.11 for the reactions of benzhydryl chlorides with deuterated pyrrolidine in MeCN (S. Chang, H. J. Koh, B. S. Lee and I. Lee, *J. Org. Chem.*, 1995, **60**, 7760). The obtained order of 1.1 is consistent with the typical value of the secondary normal β-DKIEs. (; T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, 1987, p. 239).

29 The anilinolysis of **1′** proceeds through a concerted mechanism, while that of **1** proceeds through a stepwise mechanism with a rate-limiting leaving group departure from the intermediate. One might think that the comparison of **1′** with **1** is not reasonable, since the observed k_H/k_D of **1′** reflects the bond formation rate constant (k_a) while that of **1** reflects the leaving group expulsion rate constant (k_b) from the intermediate in eqn (6). The argument can be clear that the anilinolysis of Y-*O*-aryl methyl phosphonochloridothioates proceeds through a stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving backside attack for weaker nucleophiles.

30 As mentioned earlier, the magnitudes of ρ_{XZ} values (= ~0.35) of **1** (ρ_{XZ} = +0.37) and **2** (ρ_{XZ} = +0.34) suggest the possibility of a partial participation of frontside nucleophilic attack. However, the magnitude of ρ_{XZ} value reflects the distance between nucleophile (X) and leaving group (Z). The decisive clue of the degree of participation of a hydrogen-bonded, four-center-type TS II is the magnitude ofk_H/k_D (greater than unity) value. Thus, the authors conclude that the anilinolysis of **2** (k_H/k_D = 1.15–1.29) predominantly proceeds through TS II, while that of **2** (k_H/k_D = 1.03–1.17) proceeds through TS II and III.