Kinetics and mechanism of the aminolysis of aryl ethyl chloro and chlorothio phosphates with anilines†

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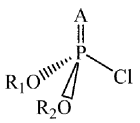
The reactions of ethyl Y-phenyl chloro (**1**) and chlorothio (**2**) phosphates with X-anilines in acetonitrile at 55.0 °C are studied kinetically and theoretically. Kinetic results yield the primary kinetic isotope effects (k_H/k_D = 1.07–1.80 and 1.06–1.27 for **1** and **2**, respectively) with deuterated aniline ($XC_6H_4ND_2$) nucleophiles, and the cross-interaction constants $\rho_{XY} = -0.60$ and -0.28 for **1** and **2**, respectively. A concerted mechanism involving a partial frontside attack through a hydrogen-bonded, four-center-type transition state is proposed. The large ρ_X ($\rho_{nuc} = -3.1$ to -3.4) and β_X (β_{nuc} = 1.1–1.2) values seem to be characteristic of the anilinolysis of phosphates and thiophosphates with the Cl leaving group. Because of the relatively large size of the aniline nucleophile, the degree of steric hindrance could be the decisive factor that determines the direction of the nucleophilic attack to the phosphate and thiophosphate substrates with the relatively small-sized Cl leaving group.

Introduction

Organophosphate and thiophosphate compounds have useful biological activities as insecticides, herbicides, acaricides, fungicides, bactericides, microbicides, nematocides and plant growth regulators.[1] So phosphoryl transfers from phosphates and thiophosphates are an important class of reaction and a considerable amount of work has been done to elucidate the mechanism.[2]

In our preceding papers,[3] we reported several phosphoryl and thiophosphoryl transfer reactions. Anilinolyses of aryl phenyl chlorophosphates (**3**),[3a] 4-chlorophenyl aryl chlorophosphates (**3′**),[3b] aryl phenyl chlorothiophosphates (**4**),[3c] and 4-chlorophenyl aryl chlorothiophosphates (**4′**)[3c] were studied kinetically in acetonitrile at 55.0 °C. Continuing our studies of the anilinolyses of phosphates and thiophosphates, we have carried out kinetic studies of the reactions of ethyl Y-phenyl chloro (**1**) and chlorothio (**2**) phosphates with X-anilines in acetonitrile at 55.0 °C to clarify the anilinolysis mechanism and stereochemistry by comparing the reactivity, the sign and magnitude of the cross-interaction constants, the steric effects, the activation parameters, and finally the kinetic isotope effects, k_H/k_D, with those obtained in the previous work.[3a–c] To support the steric effects on the stereochemistry of the studied phosphoryl and thiophosphoryl transfer reactions, the rotation barriers of phenyl, phenoxy, and/or ethyl groups of unsubstituted **1**, **2**, **3**, and/or **4** are calculated theoretically using the RHF/6-31G* level of theory.



1: A = O, $R_1 = C_6H_4Y$, $R_2 = C_2H_5$
2: A = S, $R_1 = C_6H_4Y$, $R_2 = C_2H_5$
3: A = O, $R_1 = C_6H_4Y$, $R_2 = C_6H_5$
3′: A = O, $R_1 = C_6H_4Y$, R_2 = 4-ClC_6H_4
4: A = S, $R_1 = C_6H_4Y$, $R_2 = C_6H_5$
4′: A = S, $R_1 = C_6H_4Y$, R_2 = 4-ClC_6H_4

Results and discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obeyed eqn (1) with negligible k_0 (≈0) in acetonitrile. The clean second-order rate constants, k_2, were obtained as the slope of the plot of k_{obsd} against aniline concentration.

$$k_{obsd} = k_0 + k_2[An] \quad (1)$$

Second-order rate constants, k_2, for the reactions of ethyl Y-phenyl chloro (**1**) and chlorothio (**2**) phosphates with X-anilines in acetonitrile at 55.0 °C are summarized in Table 1 together with selectivity parameters, ρ_X, β_X, ρ_Y, and ρ_{XY}. The rate increases with a more electron-withdrawing substituent Y in the substrate and with a more electron-donating substituent X in the nucleophile which is consistent with a typical nucleophilic substitution reaction with negative charge development at the reaction center P in the transition state (TS).

The reaction rate of **1** is 7.1 times faster than that of **2**, while the rate of **3** (and **3′**) is 8.8 (and 8.1) times faster than that of **4** (and **4′**) when Y = H.[3a–c] Gorenstein and coworkers showed that the hydrolysis of triethyl phosphate [$(EtO)_3P{=}O$] in 0.6 M NaOH, 55% dioxane–45% D_2O at 31 °C is 12.4 times faster than that of triethyl phosphorothionate [$(EtO)_3P{=}S$].[6] Raushel and Hong reported that the hydrolysis of diethyl aryl phosphates [$(EtO)_2P(O)OPh$] in 1.0 M KOH is approximately an order of magnitude faster than that of thiophosphotriesters [$(EtO)_2P(S)OPh$].[7] The P=O substrates are generally more reactive than their P=S counterparts

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† Electronic supplementary information (ESI) available: Synthesis of substrates, product analysis with the analytical and spectroscopic data for all compounds. Detailed data of the k_H/k_D values of the anilinolysis of **1** and **2** in acetonitrile at 55.0 °C. Detailed data of the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, of the anilinolysis of **1**, **2**, **4**, and **4′**. Theoretical calculations containing the Cartesian coordinates and absolute energies [B3LYP/6-311+G(d,p) level] of optimized structures of ethyl phenyl chlorophosphate (**1**), ethyl phenyl chlorothiophosphate (**2**), 4-nitrophenyl diphenylphosphinate (**5**), 4-nitrophenyl methylphenylphosphinate (**6**), and 4-nitrophenyl dimethylphosphinate (**7**). Calculated (RHF/6-31G* level) rotation barriers of ethyl (and/or), phenyl and/or phenoxy in **1**, **2**, **3**, and **4**. Bond angles of **1**, **2**, **3**, **4**, **5**, **6**, **7**, **9f**, **10f**, **9b**, and **10b**. See DOI: 10.1039/b713167d

Table 1 Second-order rate constants ($k_2 \times 10^4/M^{-1}\ s^{-1}$) and selectivity parameters[a] of the aminolysis of ethyl Y-phenyl chloro (**1**) and chlorothio (**2**) phosphates with X-anilines in acetonitrile at 55.0 °C

		Y					
Substrate	X	4-CH_3O	4-CH_3	H	3-CH_3O	4-Cl	ρ_Y[d]
1	4-CH_3O	113	139	182	246	328	0.90
	4-CH_3	46.0	57.0	70.4	82.4	121	0.77
	H	15.4	16.2	20.0	25.8	37.4	0.75
	4-Cl	2.60	3.00	3.60	4.80	6.00	0.72
	3-Cl	1.20	1.40	1.60	1.70	2.00	0.41
	$-\rho_X$[b]	3.09	3.13	3.21	3.29	3.40	ρ_{XY}[e] = −0.60
	β_X[c]	1.09	1.10	1.13	1.16	1.20	
		Y					
Substrate	X	4-CH_3O	4-CH_3	H	4-Cl	4-CN	ρ_Y[h]
2	4-CH_3O	16.7	17.1	25.9	53.7	112	0.95
	4-CH_3	6.57	7.92	8.99	14.5	44.7	0.89
	H	2.39	2.53	2.80	5.31	13.9	0.86
	4-Cl	0.320	0.333	0.410	1.10	1.55	0.82
	3-Cl	0.173	0.182	0.240	0.298	0.853	0.74
	$-\rho_X$[f]	3.14	3.18	3.21	3.32	3.40	ρ_{XY}[i] = −0.28
	β_X[g]	1.10	1.12	1.13	1.17	1.19	

[a] The σ values were taken from ref. 4. The pK_a values were taken from ref. 5. [b] Correlation coefficients (r) were better than 0.998. [c] $r \geq 0.996$. [d] $r \geq 0.962$. [e] $r = 0.996$. [f] $r \geq 0.991$. [g] $r \geq 0.990$. [h] $r \geq 0.955$. [i] $r = 0.990$.

for several reasons, the so-called "thio effect", which is mainly the electronegativity difference between O and S, favoring O over S.[2i,8]

The phenoxy group ($\sigma_I = 0.40$) has a stronger electron-withdrawing ability than the ethoxy group ($\sigma_I = 0.28$).[9] Solely considering the difference of inductive effects between the phenoxy and ethoxy group, the positive charge of the reaction center P in **1** (and **2**) would be smaller than that in **3** (and **4**). If the rate is proportional to the positive charge on the reaction center P, the rate ratios of $k_{P=O}(\mathbf{1})/k_{P=O}(\mathbf{3}) < 1$ and $k_{P=S}(\mathbf{2})/k_{P=S}(\mathbf{4}) < 1$ should be obtained. To the contrary, rate ratios of $k_{P=O}(\mathbf{1})/k_{P=O}(\mathbf{3}) = 2.2$ and $k_{P=S}(\mathbf{2})/k_{P=S}(\mathbf{4}) = 2.8$ are obtained experimentally. Fig. 1 shows the natural bond order (NBO) charges on the reaction center P, 2.233 (**1**), 2.230 (**3**); 1.687 (**2**), 1.661 (**4**). The NBO charges of the reaction center P are not consistent with expectations for the inductive effects and do not explain the obtained rate ratios explicitly.

Let us define 'the degree of distortion' of **1**, **2**, **3**, and **4** from the regular tetrahedral structure, as eqn. (2),

$$\Delta\delta = \sum |\theta_c - \theta_i| / \theta_i = \sum |\theta_c - 109.5| / 109.5 \qquad (2)$$

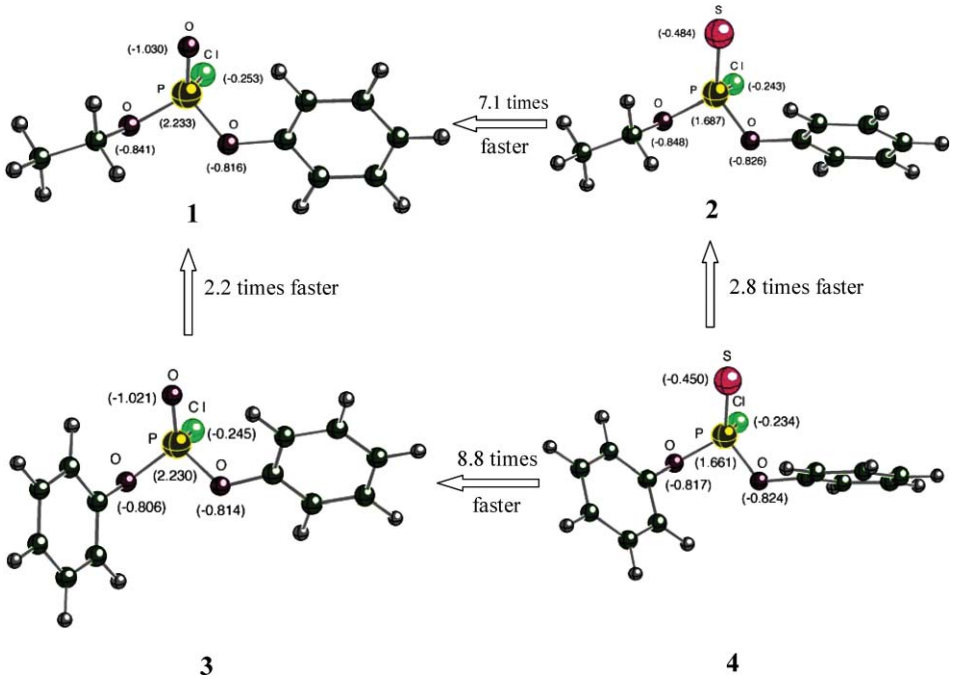
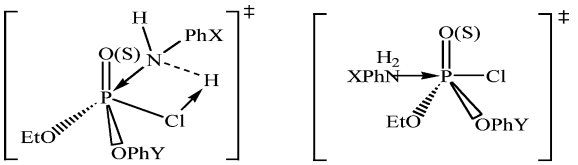


Fig. 1 The B3LYP/6-311+G(d,p)[10] geometries and NBO charges of **1**, **2**, **3**,[3a] and **4**[3c] with Y = H. The relative rates are for unsubstituted aniline at 55.0 °C.

where $\Delta\delta$ is the degree of distortion, $\sum$ means the sum of all of six bond angles, θ_c is the calculated bond angle using the B3LYP/6-311+G(d,p) level,[10] and θ_i is the ideal bond angle (109.5°) of a regular tetrahedral structure. The $\Delta\delta$ values of **1**, **2**, **3**, and **4** are 0.38, 0.45, 0.40, and 0.48, respectively. Due to the larger size of P=S sulfur compared to that of P=O oxygen, the distortion of P=S substrates (**2** and **4**) is larger than that of P=O substrates (**1** and **3**), and due to the larger size of phenoxy ligand compared to that of ethoxy ligand, **3** (and **1**) is more distorted than **4** (and **2**). The detailed bond angles of **1**, **2**, **3**, and **4** are summarized in the ESI.

We have previously proposed a backside nucleophilic attack concerted mechanism with a late, product-like TS for the anilinolysis of **3** in acetonitrile on the basis of the large ρ_X (and β_X), the especially large negative cross-interaction constant ($\rho_{XY} = -1.31$), and the small value of the secondary inverse kinetic isotope effects (KIEs), $k_H/k_D = 0.61$–0.87, with deuterated aniline nucleophiles ($XC_6H_4ND_2$).[3a] In contrast, a concerted mechanism involving a partial participation of a frontside nucleophilic attack through a hydrogen-bonded, four-center type TS was proposed for the anilinolysis of **4** and **4′** in acetonitrile for several reasons, mainly the primary KIEs, $k_H/k_D = 1.11$–1.33 and 1.10–1.46 for **4** and **4′**, respectively.[3c] The KIEs with deuterated anilines in the present work are summarized in Table 2 (detailed data is available in the ESI). As observed in the anilinolysis of **4** and **4′**,[3c] the k_H/k_D values of **1** (1.07–1.80) and **2** (1.06–1.27) all show primary normal KIEs, indicating that the partial deprotonation of the aniline nucleophile occurs in the rate-limiting step by hydrogen bonding. A concerted mechanism involving a partial frontside nucleophilic attack through a hydrogen-bonded, four-center-type TS **I** accompanied by a backside nucleophilic attack with a trigonal bipyramidal pentacoordinate (TBP-5C) TS **II** is proposed in the present work, for the same reasons as in the anilinolysis of **4** and **4′**.[3c]



TS I **TS II**

The observed KIEs in Table 2 would be the sum of (i) the primary normal KIE, $k_H/k_D > 1$, because of the partial deprotonation of one of the two N–H(D) bonds in the TS **I** for a frontside attack, (ii) the secondary inverse KIE, $k_H/k_D < 1$, because of the steric hindrance that increases the out-of-plane bending vibrational frequencies of the other N–H(D) bond in TS **I** for a frontside attack, (iii) the secondary inverse KIE, $k_H/k_D < 1$, because of the steric congestion that increases the vibrational frequencies of both of the N–H(D) bonds in TS **II** for a back-side attack, (iv) lowering the k_H/k_D value because of the nonlinear and unsymmetrical structure of N···H(D)···Cl in TS **I** and finally (v) lowering the k_H/k_D value because of heavy atom (N and Cl) contribution to the reaction-coordinate motion.[11] Thus, the real primary KIE due to the hydrogen bond between the hydrogen of the N–H(D) moiety and the Cl leaving group should be greater than the observed value.

Buncel and his coworkers reported that the ethanolyses of 4-NO_2PhOP(=O)(Ph)$_2$ (**5**), 4-NO_2PhOP(=O)(Ph)(Me) (**6**) and 4-NO_2PhOP(=O)(Me)$_2$ (**7**) give relative rates of 1 : 69 : 235.[12] As shown in Fig. 2, the NBO charges of the reaction center P atom, 2.117 (**5**), 2.096 (**6**), and 2.072 (**7**), are consistent with expectations for the electronic influence of the ligands, Ph ($\sigma_I = 0.12$) and Me ($\sigma_I = -0.01$) groups.[9] The plot of $\sum\sigma_I$ of two ligands, Ph + Ph (**5**), Ph + Me (**6**), and Me + Me (**7**), against the NBO charges on P atom of three phosphinates gives the slope of 5.77 with correlation coefficient, $r = 0.999$. However, the relative rates of the phosphinates are not in accord with expectations for the electronic influence of the ligands, implying the decisive role of steric effects on the reaction rates over the inductive effects of the ligands as discussed by Buncel and his coworkers.[12]

All three substrates have distorted tetrahedral conformations. The degrees of distortion, defined as eqn (2), of **5**, **6**, and **7** are $\Delta\delta = 0.28$, 0.34, and 0.32, respectively, but less than those of **1**–**4** ($\Delta\delta = 0.38$–0.48). In the case of **5**, three large ligands, two Ph and 4-nitrophenoxy, introduce the smallest distortion among the three substrates. The bond angles of **5**, **6**, and **7** are available in the ESI.

Considerably large steric effects on the ethanolysis (with free ethoxide) of the phosphinates can be rationalized by the *backside* nucleophilic attack towards the 4-NO_2PhO leaving group since the large steric effects on the reaction rates cannot be substantiated by the frontside nucleophilic attack, whether by apical(Nu)–equatorial(Lg) or eq(Nu)–ap(Lg) position in the TBP-5C TS. The aminolysis of diphenyl chlorophosphinate [ClP(=O)(Ph)$_2$; **8**] with X-anilines in acetonitrile at 55.0 °C gives primary normal KIEs, $k_H/k_D = 1.42$–$1.82 > 1$, implying major participation of the frontside nucleophilic attack with hydrogen bonding in the TS, such as TS **I**.[3c,d,13] The differences between the two reaction systems of **5** and **8** are the nucleophiles (relatively smaller ethanol in **5** compared to aniline in **8**) and the leaving groups (considerably larger 4-NO_2PhO in **5** compared to Cl in **8**). These results suggest that the direction of nucleophilic attack in phosphoryl and thiophosphoryl reactions depends on both nucleophile and leaving group.

The stereochemistry of the studied phosphoryl and thiophosphoryl transfer reactions can be rationalized by the steric effects as follows: (i) In the case of **5**, the rotations of the two bulky phenyl rings may be sterically hindered by each other, so that backside nucleophilic attack in the ethanolysis of **5** could be possible.

Table 2 Kinetic isotope effects, k_H/k_D, values of the aminolysis of ethyl Y-phenyl chloro (**1**) and chlorothio (**2**) phosphates with deuterated X-anilines in acetonitrile at 55.0 °C

X	4-CH_3O			H			4-Cl		
Y	4-CH_3O	H	4-Cl	4-CH_3	H	4-Cl	4-CH_3	H	4-Cl
1	1.09	1.19	1.22	1.10	1.28	1.80	1.07	1.10	1.25
2	1.06	1.14	1.27	1.09	1.12	1.17	1.08	1.11	1.23

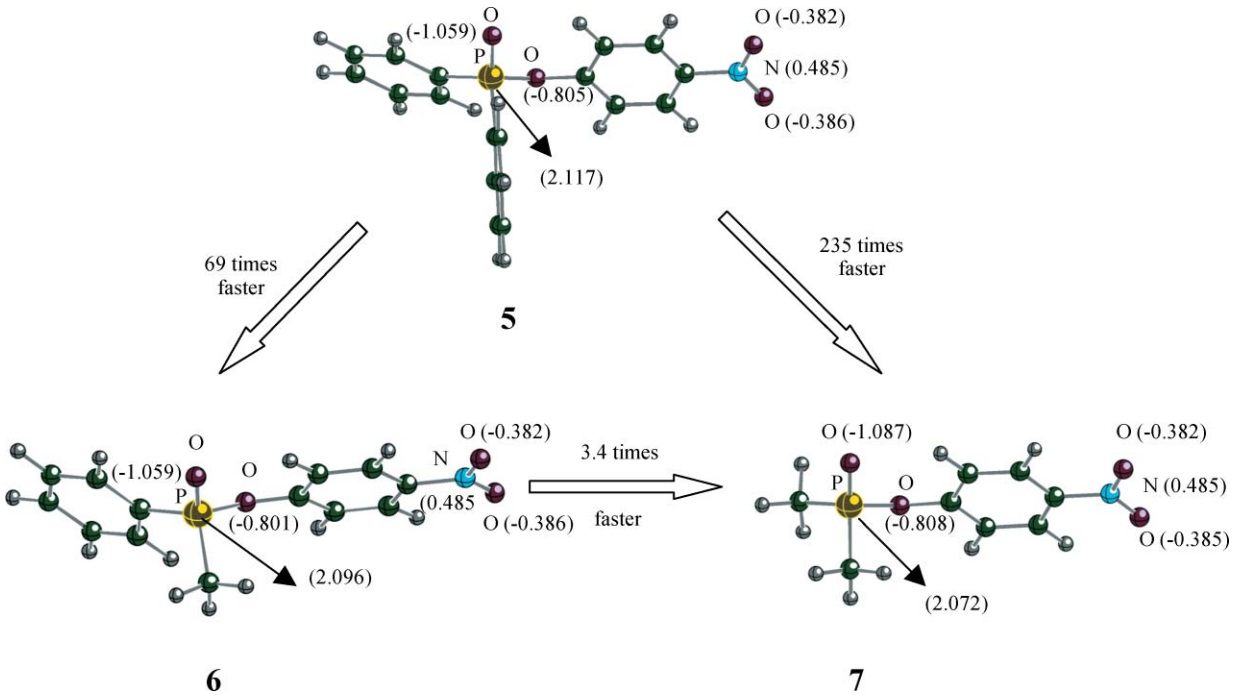


Fig. 2 The B3LYP/6-311+G(d,p)[10] geometries and NBO charges of **5**, **6**, and **7**. The relative rates are for the ethanolysis at 25.0 °C.

At a glance, this suggestion is not in accord with the proposed mechanism of the backside attack in **3** (and **3′**). The phenyl rings are directly bonded to the reaction center P atom in **5** while the intervening oxygen atoms are located between the reaction center P and two phenyl rings in **3** (and **3′**). The intervening oxygen atom may render enough backside space towards the leaving group to permit backside nucleophilic attack, but the steric hindrance is so large that very small secondary inverse KIEs, $k_H/k_D = 0.61$–0.87 (in **3**) and 0.64–0.87 (**3′**), are obtained.[3a,b] (ii) It is well known that the methyl group rotation is too fast to distinguish the NMR ^{1}H peaks of CH_3. The ethyl group of **1** and **2** would rotate very fast[14] and a backside attack would be sterically inhibited resulting in a partial frontside attack, so that primary normal KIEs, $k_H/k_D =$ 1.07–1.80 (in **1**) and 1.06–1.27 (in **2**), are obtained. (iii) Without considering phenyl ring (or phenoxy) rotation, the ground state (GS) structure of **4** shows that one of the phenyl groups could interrupt the backside attack compared to the GS of **3**, that is, the parallel phenyl group to P–Cl bond in **4** (Fig. 1) occupies sterically hindered space in the direction of a backside attack, resulting in a partial frontside attack. However, taking into account phenyl ring rotation,[15] the degree of steric hindrance to the backside attack seems to be the same in both **3** and **4**. But primary normal KIEs, $k_H/k_D = 1.11$–1.33 (in **4**) and 1.10–1.46 (in **4′**), are observed in contrast to the small secondary inverse KIEs in **3** (and **3′**). The NBO charges on the reaction center P are 2.230 in **3** and 1.661 in **4** (unsubstituted one) in the GS from the B3LYP/6-311+G(d,p)[10] level, mainly due to the electronegativity difference between O and S (Fig. 1).[3c] Considering the positive charge difference and assuming the similar steric hindrance between **3** and **4**, the backside attack in the reaction of **4** would be much slower than that of **3**. Therefore, we suggest that the smaller positive charge of the reaction center P in **4** compared to that in **3** would result in the partial participation of the frontside attack in the anilinolysis of **4** (and **4′**), contrary to the backside attack in **3** (and **3′**).

These results suggest that the degree of steric hindrance could be the decisive factor that determines the stereochemistry of the studied phosphoryl and thiophosphoryl transfer reactions, especially when the nucleophile is relatively large, such as aniline, and the leaving group is relatively small, such as Cl.

In the case of the frontside nucleophilic attack, the nucleophile and leaving group should be located adjacent to each other in order to form the hydrogen bond between the N–H(D) moiety and the Cl leaving group. Two possible TS structures for the frontside attack would be ap(Nu)–eq(Lg) or eq(Nu)–ap(Lg) in the TBP-5C. However, the MO theoretical calculation [CPCM-MP2/6-31+G(d) level] of the model reactions of dimethyl chloro (**9**) and chlorothio (**10**) phosphates with ammonia in acetonitrile shows that the TS structure for the frontside attack has a very distorted TBP-5C, which is even hard to call TBP-5C.[3c] As shown in Fig. 3, in **9f** (frontside attack), when we adopt the ap(Nu)–eq(Lg) TS, the bond angle of two apical positions is 145.1°, while when adopting the eq(Nu)–ap(Lg) TS, the bond angle of two apical positions is 135.4°, far from the ideal bond angle 180°. In the case of **10f**, angles of 142.0° and 136.5°, also far from 180°, are given for ap(Nu)–eq(Lg) and eq(Nu)–ap(Lg) TS, respectively. The differences between ap(Nu)–eq(Lg) and eq(Nu)–ap(Lg) TS are only 9.6° and 5.5° for **9f** and **10f**, respectively. In the case of backside attack, the bond angles of two apical positions are 174.0° and 168.9°, not far from 180°, for **9b** and **10b**, respectively.

Let us define again the degree of distortion, $\Delta\delta$, from the ideal TBP-5C TS as eqn (3).

$$\Delta\delta = \sum[|\theta_c - \theta_i|/\theta_i]_{e,e} + \sum[|\theta_c - \theta_i|/\theta_i]_{a,e} = \sum[|\theta_c - 120|/120]_{e,e} + \sum[|\theta_c - 90|/90]_{a,e} \quad (3)$$

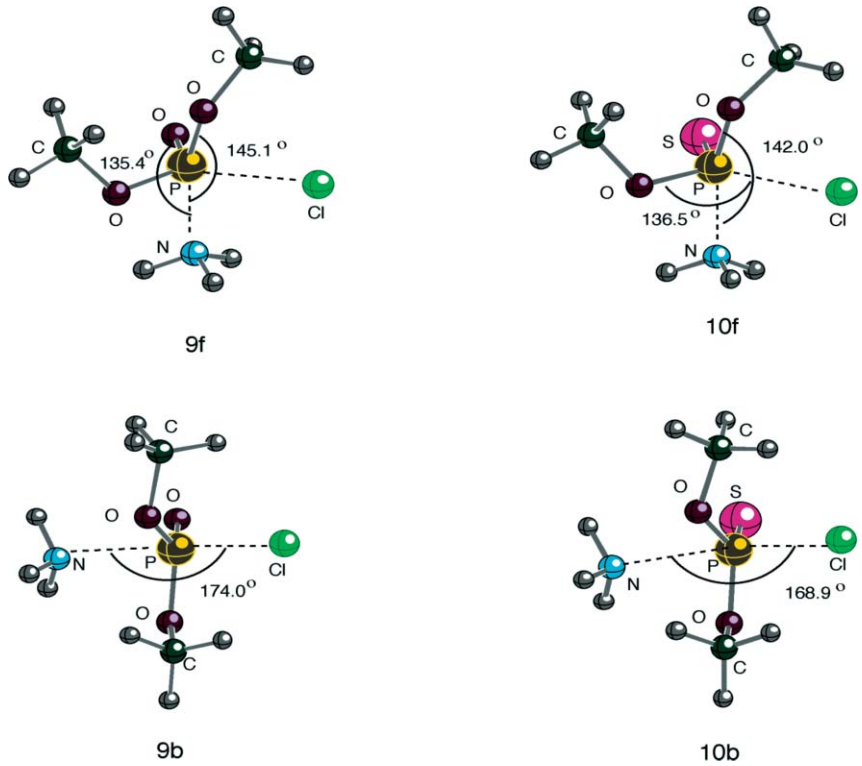


Fig. 3 TS structures and bond angles optimized at the CPCM-MP2/6-31+G(d) level of theory for the reactions of (**9f**) **9** (frontside attack), (**10f**) **10** (frontside attack), (**9b**) **9** (backside attack), and (**10b**) **10** (backside attack) with ammonia in acetonitrile.[3c]

The first term on the right side is the sum of the bond angle deviations from the ideal bond angle of 120° for the three equatorial ligands (subscript e,e) and the second term is the sum of six bond angle deviations from the ideal bond angle of 90° between apical and equatorial ligands (subscript a,e). In the case of **9f** and **10f**, we choose the two apical ligands that have the largest bond angle. The degrees of distortion for **9f**, **10f**, **9b**, and **10b** are $\Delta\delta = 0.97$, 1.03, 0.64, and 0.68, respectively. These results show that the P=S system has a larger $\Delta\delta$ value compared to the P=O system and that the degree of distortion of a frontside attack is considerably larger than that of a backside attack from the ideal TBP-5C TS. These calculated results of the model reactions strongly suggest that the conformation of the TS structure of the frontside nucleophilic attack must be very distorted, which is even hard to call TBP-5C since the ligands of the studied substrates are considerably larger than those of the model compounds. The detailed bond angles of **9f**, **10f**, **9b**, and **10b** are summarized in the ESI.

Now the rate ratios of $k(\mathbf{1})/k(\mathbf{3}) \approx 2$–4 (P=O systems) and $k(\mathbf{2})/k(\mathbf{4}) \approx 2$–7 (P=S systems) can be substantiated by the steric effects over the electronic effects of the ligands. The faster rate of **2** with ethoxy and phenoxy ligands compared to that of **4** with two phenoxy ligands can be explained by steric effects since the two reactions proceed by the same partial participation of frontside attack; thus less steric hindrance results in faster rate. However, the faster rate of **1** compared to that of **3** due to less steric hindrance is not adequate since the aniline attacks backside in the anilinolysis of **3**, while the aniline attacks frontside and backside towards the Cl leaving group in the anilinolysis of **1**. For the backside attack in the reaction of **3**, the steric hindrance in the bond formation should be so large that the reaction rate would be retarded. In the reactions of **1**, the rate of the backside attack would be retarded due to the large steric hindrance and the rate of the frontside attack would be comparable with the backside attack. As a result, the contribution of a frontside attack in **1** with less steric hindrance leads to $k(\mathbf{1})/k(\mathbf{3}) \approx 2$–4.

As shown in Table 3, the large Hammett ρ_X ($\rho_{nuc} = -3.1$ to -4.6) and Brønsted β_X ($\beta_{nuc} = 1.1$–1.7) values of the anilinolysis of the studied reaction systems (**1**–**4′**) suggest extensive bond formation in the TS. These values are considerably larger than those of other nucleophilic substitution reactions of phosphate and thiophosphate systems in which the reactions proceed by a concerted mechanism: reaction ($\beta_X = \beta_{nuc}$); pyridinium-*N*-phosphonate with pyridines (0.53);[16a] 3-methoxy pyridino-*N*-phosphate

Table 3 Summary of k_2 ($\times 10^4$/M^{-1} s^{-1}), selectivity parameters, activation parameters, and k_H/k_D values of the anilinolysis of (EtO)(YPhO)P(O)Cl (**1**), (EtO)(YPhO)P(S)Cl (**2**), (PhO)(YPhO)P(O)Cl (**3**), (4-ClPhO)(YPhO)-P(O)Cl (**3′**), (PhO)(YPhO)P(S)Cl (**4**), and (4-ClPhO)(YPhO)P(S)Cl (**4′**) in Acetonitrile at 55.0 °C

	1	**2**	**3a**	**3′**[b]	**4c**	**4′**[c]
k_2[d]	20.0	2.80	8.91	12.0	1.01	1.48
$-\rho_X$	3.1–3.4	3.2–3.4	3.4–4.6	4.0–4.2	3.8–4.0	3.5–3.9
β_X	1.1–1.2	1.1–1.2	1.1–1.7	1.4–1.5	1.3–1.4	1.2–1.4
ρ_Y	0.4–0.9	0.8–1.0	0.2–0.9	0.1–0.3	0.7–0.9	0.5–0.9
$-\rho_{XY}$	0.60	0.28	1.31	0.31	0.22	0.50
$\Delta H^{\ddagger}$[e]	2–8[g]	~5[g]	2–10	2–3	7–13[g]	4–11[g]
$-\Delta S^{\ddagger}$[f]	47–64[g]	54–64[g]	43–65	60–68	32–54[g]	48–61[g]
k_H/k_D	1.1–1.8	1.1–1.3	0.6–0.9	0.6–0.9	1.1–1.3	1.1–1.5

[a] Ref. 3*a*. [b] Ref. 3*b*. [c] Ref. 3*c*. [d] For X = Y = H. [e] kcal mol^{-1}. [f] cal mol^{-1} K^{-1}. [g] Detailed data is available in the ESI.

with pyridines (0.17);[16b] isoquinolino-*N*-phosphonate with pyridines (0.15);[16c] phosphorylated 3-methoxypyridine with pyridines (0.17)[16d] and primary amines (0.19);[16d] phosphorylated 4-morpholinopyridine with pyridines (0.22),[16d] primary amines (0.28)[16d] and quinuclidines (−0.01);[16e] 4-nitrophenyl phosphate with quinuclidines (−0.05);[16e] 2,4-dinitrophenyl phosphate with quinuclidines (−0.10);[16e] phosphorylated pyridine with quinuclidines (−0.10)[16e] (negative β_{nuc} values are ascribed to desolvation of quinuclidines before nucleophilic attack) and anionic oxygens (0.3);[16f] acetyl phosphate dianion with pyridines (0.10);[16f] 4-nitrophenyl diphenyl phosphate with phenolate anions (0.53);[16g] 2,4-dinitrophenyl diphenyl phosphate with phenolate anions (0.12);[16h] *O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate with anionic oxygens (0.49; linear part with phenoxides);[16i] 2-aryloxy-2-oxo-1,3,2-dioxaphosphorinans (aryl = 2,4-dinitrophenyl) with pyridines (0.61)[16j] and oxyanions (0.32, 0.37, 0.42, 0.48, aryl = 2,4-dinitrophenyl, 4-acetyl-2-nitrophenyl, 4-chloro-2-nitrophenyl and 4-nitrophenyl, respectively);[16j] 2,4-dinitrophenyl methyl phosphate monoanion with oxyanions (0.31),[16k] pyridines (0.31)[16k] and primary amines (0.31);[16k] bis 2,4-dinitrophenyl phosphate monoanion with pyridines (0.54);[16l] hydrolysis of phosphorylethanolamine with intramolecular nucleophilic amine participation (0.7),[16m] aryl phenyl chlorophosphate with pyridines (0.16–0.18);[3e] aryl bis(4-methoxyphenyl) phosphate with pyridines (biphasic; 0.09–0.14 for stronger nucleophiles and 0.22–0.39 for weaker nucleophiles);[3f] and aryl phenyl isothiocyanophosphate with pyridines (1.13–1.28).[3g] For the studied phosphoryl and thiophosphoryl transfer reactions, the large ρ_X (−3.1 to −4.6) and β_X (1.1–1.7) values seem to be characteristic of the anilinolysis of phosphates and thiophosphates with the Cl leaving group.

The ρ_Y values of the anilinolysis of the studied substrates in Table 3 have similar magnitudes except **3′** with its smaller value of $\rho_Y = 0.1$–0.3 because of the electron shunt toward the electron acceptor equatorial ligand (4-ClPhO) in the TS.[3b]

Fig. 4 shows the plots of ρ_X *vs.* σ_Y and ρ_Y *vs.* σ_X for the anilinolysis of **1** and **2** with good linearities. The negative ρ_{XY} values (−0.60 and −0.28 for **1** and **2**, respectively) imply rate-limiting nucleophilic bond formation. A more electron-withdrawing substituent ($\partial\sigma_Y > 0$) in the substrate leads to a greater degree of bond formation ($\partial\rho_X < 0$ or $|\partial\rho_X| > 0$), resulting in $\rho_{XY} = \partial\rho_X/\partial\sigma_Y < 0$, and a stronger nucleophile ($\partial\sigma_X < 0$) leads to greater negative charge development at the reaction center ($\partial\rho_Y > 0$) because of greater bond formation, resulting in $\rho_{XY} = \partial\rho_Y/\partial\sigma_X < 0$. The negative sign of ρ_{XY} is in agreement with the proposed concerted mechanism.[17]

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (2a)$$

$$\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \quad (2b)$$

The magnitude of the ρ_{XY} value is inversely proportional to the distance between X and Y,[17] *i.e.*, a larger magnitude of the ρ_{XY} value results from a greater degree of bond formation. The magnitude of ρ_{XY} in the P=O system is greater than that in the P=S system: $|\rho_{XY}$ (**1**)$| = 0.60 > |\rho_{XY}$ (**2**)$| = 0.28$ and $|\rho_{XY}$ (**3**)$| = 1.31 > |\rho_{XY}$ (**4**)$| = 0.22$. The smaller magnitude of ρ_{XY} (**3′**) than that of ρ_{XY} (**4′**) was explained by the electron shunt toward the equatorial ligand (4-ClPhO) in the TS of **3′**.[3b] On the basis of the magnitudes of ρ_{XY}, the degree of bond formation in the TS would be **3** > **1** > **2** ≥ **4** despite the comparable magnitudes of ρ_X (and β_X) of **1**, **2**, **3**, and **4**. These experimental ρ_X (and β_X) values demonstrate that the magnitudes of ρ_X (and β_X) alone cannot provide conclusive evidence for the degree of bond formation in the TS.

The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) of all substrates, **1**–**4′**, in Table 3 have comparable magnitudes. The small $\Delta H^{\ddagger}$ values and large negative $\Delta S^{\ddagger}$ values are characteristic of a relatively late TS with a large degree of bond formation and breaking. Since the Cl leaving group is a strong nucleofuge, a large degree of bond breaking will not require a lot of energy and a large degree of bond formation will provide partial bond energy in the TS, resulting in small positive $\Delta H^{\ddagger}$ values. The large negative $\Delta S^{\ddagger}$ values may result from a large degree of bond breaking and also steric hindrance in the bond formation of aniline.

Experimental section

Materials

The starting materials, ethyl dichlorophosphate (for **1**), ethyl dichlorothiophosphate (for **2**), phenols and triethylamine were G.R. grade and were used without further purification. The other materials are the same as previously described.[3c]

Kinetic procedure

The second-order rate constants (k_2) and pseudo-first-order rate constants, k_{obsd}, were determined as previously described[3a–c] with

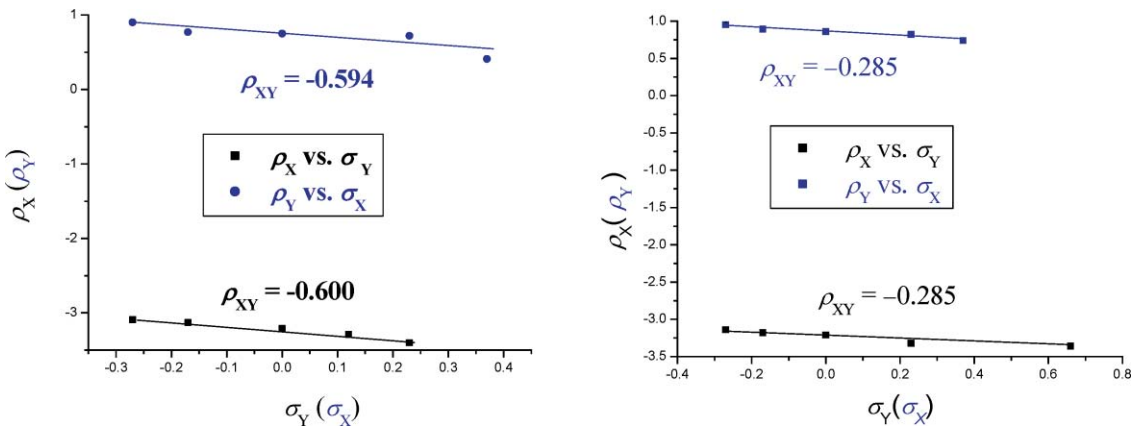


Fig. 4 The plots of ρ_X *vs.* σ_Y and ρ_Y *vs.* σ_X of the reactions of substrates, **1** and **2**, with X-anilines in acetonitrile at 55.0 °C.

a large excess of anilines: [aniline] = 0.1–0.3 M; [substrate] = 5×10^{-3} and 1×10^{-3} M for **1** and **2**, respectively.

Conclusions

Partial participation of a frontside attack concerted mechanism through a hydrogen-bonded four-center-type TS **I**, as well as in the anilinolysis of **4** and **4′**,[3c] is proposed for the aminolysis of ethyl phenyl chloro (**1**) and chlorothio (**2**) phosphates with anilines in acetonitrile at 55.0 °C. This proposal is on the basis of (i) the negative ρ_{XY} value, ρ_{XY} (**1**) = −0.60 and ρ_{XY} (**2**) = −0.28, (ii) the primary kinetic isotope effects, k_H/k_D (**1**) = 1.07–1.80 and k_H/k_D (**2**) = 1.06–1.27, (iii) steric inhibition of backside nucleophilic attack, supported by the theoretical calculation results, and (iv) small $\Delta H^{\ddagger}$ with large negative $\Delta S^{\ddagger}$ values.

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13 The k_H/k_D (=1.42–1.82) values in **6** are somewhat larger than those of other phosphoryl and thiophosphoryl transfers in Table 3, so the "major" participation of the frontside nucleophilic attack may be acceptable.

14 The methyl group rotation barrier is known to be *ca.* 3 kcal mol^{-1} Y. Xue, M. S. Pavlova, Y. E. Ryabov, B. Reif and N. R. Skrynnikov, *J. Am. Chem. Soc.*, 2007, **129**, 6827. The calculated (RHF/6-31G* level of theory) ethyl group rotation barriers of unsubstituted substrates in the gas phase are 6.2 (**1**) and 5.6 kcal mol^{-1} (**2**) when the remaining part except the ethyl group is fixed, but 3.1 (**1**) and 3.4 kcal mol^{-1} (**2**) when the conformations are changed with the ethyl group rotations. These results may show that the free rotation of ethyl group is very fast. Detailed data are available in the ESI.

15 The calculated (RHF/6-31 G* level of theory) phenyl group rotation barriers of unsubstituted substrates in the gas phase are 1.6 (**3**) and 2.4 kcal mol^{-1} (**4**) when the remaining part except one phenyl group is fixed, but 2.9 (**3**) and 3.8 kcal mol^{-1} (**4**) when the conformations are changed with the phenyl group rotations. The calculated phenoxy group rotation barriers are 18.8 (**3**) and 45.4 kcal mol^{-1} (**4**) when the remaining part, except one phenoxy group, is fixed. These results may show that the free rotations of phenyl or phenoxy group are also very fast. Detailed data is available in the ESI. House, and his coworkers reported the rotation barriers of 1,8-diarylanthracene derivatives by variable temperature NMR as 5.3–10.4 kcal mol^{-1} (H. O. House, J. A. Hrabie and D. VanDerveer, *J. Org. Chem.*, 1986, **51**, 921), and Mazzanti and his coworkers reported the rotation barriers of *ca.* 16 kcal mol^{-1} by using MMFF force field (L. Lunazzi, M. Mancinelli and A. Mazzanti, *J. Org. Chem.*, 2007, **72**, 5391).

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