Concurrent primary and secondary deuterium kinetic isotope effects in anilinolysis of *O*-aryl methyl phosphonochloridothioates†

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The nucleophilic substitution reactions of Y-*O*-aryl methyl phosphonochloridothioates with substituted anilines ($XC_6H_4NH_2$) and deuterated anilines ($XC_6H_4ND_2$) are investigated kinetically in acetonitrile at 55.0 °C. The Hammett and Brønsted plots for substituent (X) variations in the nucleophiles are biphasic concave downwards with a break region between X = H and 4-Cl. The deuterium kinetic isotope effects (DKIEs) are primary normal ($k_H/k_D = 1.03–1.30$) for stronger nucleophiles (X = 4-MeO, 4-Me and H), and *extremely large* secondary inverse ($k_H/k_D = 0.367–0.567$) for weaker nucleophiles (X = 4-Cl, 3-Cl and 3-NO₂). The cross-interaction constants are negative ($\rho_{XY(H)} = -0.95$ and $\rho_{XY(D)} = -1.11$) for stronger nucleophiles, while positive ($\rho_{XY(H)} = +0.77$ and $\rho_{XY(D)} = +0.21$) for weaker nucleophiles. These kinetic results indicate that the mechanism changes from a concerted process involving frontside nucleophilic attack for stronger nucleophiles to a stepwise process with a rate-limiting leaving group expulsion from the intermediate involving backside attack for weaker nucleophiles. A hydrogen-bonded, four-center-type transition state (TS) is suggested for a frontside attack, while a trigonal bipyramidal pentacoordinate TS is suggested for a backside attack. The *unusually small* DKIEs, as small as or equal to 0.4, for weaker nucleophiles seem to be ascribed to severe steric congestion in the TS.

Introduction

Kinetic isotope effects (KIEs) provide one of the most powerful tools for the elucidation of reaction mechanisms.[1] KIEs can give information about the transition state (TS) structure and can indicate the rate-limiting step in a reaction.[2]

In this respect, deuterium kinetic isotope effects (DKIEs) involving deuterated aniline ($XC_6H_4ND_2$) nucleophiles have provided a useful means to determine the TS structures in nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures. Incorporation of deuterium in the nucleophile has an advantage in that the α-DKIEs reflect only the degree of bond formation. When partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding, the k_H/k_D values are greater than unity. In contrast, DKIEs can only be inverse ($k_H/k_D < 1.0$) in a normal S_N2 reaction, since the N–H(D) vibrational frequencies invariably increase upon going to the TS because of an increase in steric congestion in the bond-making process.[3] Thus, the greater the extent of bond formation, the smaller the k_H/k_D value becomes.

We have reported the DKIEs for the reactions of various substrates[4] with deuterated amines to clarify the reaction mechanism. Some special results we have obtained are as follows: (i) the max. value of primary normal DKIE, $k_H/k_D = 2.58$, for the reactions of benzyl benzenesulfonates with deuterated anilines in MeOH.[5] (ii) The min. value of secondary inverse DKIE, $k_H/k_D = 0.739$, for the reactions of phenylchloroformates with deuterated anilines in MeCN.[6] (iii) The max. values of primary normal DKIEs, $k_H/k_D \approx 2.7$, for the nucleophilic addition reactions of deuterated benzylamines to benzylidenemalonitriles,[7] β-nitrostilbene[8] and ethyl-α-cyanocinnamates[9] in MeCN. (iv) The min. value of secondary inverse DKIE, $k_H/k_D = 0.803$, for the reactions of *N*-methyl-*N*-phenylcarbamoyl chlorides with deuterated benzylamines in MeCN.[10] (v) The secondary normal β-type-DKIEs, $k_H/k_D > 1$, when the rate-determining step is the breakdown of the intermediate: $k_H/k_D = 1.03–1.11$ for the reactions of phenylacetyl chlorides with deuterated anilines in MeCN,[11] $k_H/k_D = 1.04–1.12$ for the reactions of 4-nitrophenyl *N*-phenylcarbamates with deuterated benzylamines in MeCN[12] and $k_H/k_D = 1.02–1.11$ for the reactions of benzhydryl chlorides with deuterated pyrrolidine in MeCN.[13] The obtained order of 1.1 is consistent with the typical value of secondary normal β-DKIEs.[14]

Cross-interaction constants (CICs), ρ_{XY}, can be also a strong tool to provide the mechanistic criteria for the nucleophilic substitution reactions.[15]

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \qquad (1a)$$

$$\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \qquad (1b)$$

Here, X and Y are the substituents of the nucleophiles and substrates, respectively. 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. The sign of ρ_{XY} is normally negative in a concerted S_N2 reaction (or in a stepwise reaction with rate-limiting bond formation), whereas it is positive for a stepwise reaction with a rate-limiting leaving group departure from the intermediate. The magnitude of ρ_{XY} in a concerted S_N2

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Table 1 Summary of selectivity parameters (ρ_X, β_X, ρ_Y and ρ_{XY}), deuterium kinetic isotope effects (k_H/k_D) and proposed mechanisms for the reactions of $R_1R_2P(=A; A = O$ or $S)Cl$ with $XC_6H_4NH_2(D_2)$ in acetonitrile at 55.0 °C

A(R_1,R_2)[a]	$-\rho_X$	β_X	ρ_Y	ρ_{XY}	k_H/k_D	Proposed mechanism	ref.
O(YPhO,PhO)	3.42–4.63	1.24–1.68	0.22–0.87	−1.31	0.61–0.87	Concerted S_N2; late TS; mainly backside attack[d]	18a
S(YPhO,PhO)	3.81–4.01	1.34–1.41	0.67–0.89	−0.22	1.11–1.33	Concerted S_N2; backside and frontside attack[e]	18c
O(YPhO,EtO)	3.09–3.40	1.09–1.20	0.41–0.90	−0.60	1.07–1.80	Concerted S_N2; backside and frontside attack	18f
S(YPhO,EtO)	3.14–3.40	1.10–1.19	0.74–0.95	−0.28	1.06–1.27	Concerted S_N2; backside and frontside attack	18f
O(EtO,EtO)	2.99/2.80[b]	1.06/0.993	—	—	0.714–0.919	Concerted S_N2; mainly backside attack	18g
S(EtO,EtO)	2.75/2.70	0.977/0.957	—	—	1.01–1.10	Concerted S_N2; backside and frontside attack	18g
O(MeO,MeO)	2.72/2.56	0.962/0.907	—	—	0.798–0.979	Concerted S_N2; backside and frontside attack	18g
S(MeO,MeO)	2.81/2.73	0.993/0.963	—	—	0.945–1.06	Concerted S_N2; backside and frontside attack	18g
S(YPhS,Ph)	3.35–3.47	1.21–1.25	0.29–0.50	−0.31	1.15–1.59	Concerted S_N2; mainly frontside attack	18h
O(Ph,Ph)	4.78/4.56	1.69/1.62	—	—	1.42–1.82	Concerted S_N2; mainly frontside attack	18d
S(Ph,Ph)	3.97/3.94	1.40/1.40	—	—	1.00–1.10	Concerted S_N2; backside and frontside attack	18e
O(Ph,Me)	2.49/2.28	0.88/0.81	—	—	1.62–2.10	Concerted S_N2; mainly frontside attack	18i
O(Me,Me)[c]	4.59/4.42	1.62/1.56	—	—	0.703–0.899	Concerted S_N2; mainly backside attack	18i

[a] The substrates, $R_1R_2P(=O)Cl$ and $R_1R_2P(=S)Cl$, are denoted as O(R_1R_2) and S(R_1R_2), respectively. [b] Calculated from k_H/calculated from k_D. [c] Selectivity parameters and DKIEs are at 15.0 °C. [d] Backside attack indicates that the reaction proceeds through in-line type TS I. [e] Frontside attack indicates that the reaction proceeds through a hydrogen-bonded, four-center-type TS II.

reaction is inversely proportional to the distance between X and Y in the TS.

There is extensive literature on phosphoryl transfer reactions and two main types of mechanisms are known to occur, stepwise (A_N+D_N) and concerted (A_ND_N).[16] The attacking direction of the nucleophile can be backside and/or frontside depending upon substrate, nucleophile, leaving group and reaction conditions.[17] Two possible TS structures of frontside nucleophilic attack would be apical(Nu)-equatorial(Lg) or eq(Nu)-ap(Lg) in the trigonal bipyramidal pentacoordinate (TBP-5C), while that of backside attack is ap(Nu)-ap(Lg).

In our preceding papers, we reported the anilinolysis of phosphate derivatives in MeCN, and proposed a reaction mechanism based mainly on the DKIEs and CICs.[18] In Y-aryl phenyl chlorophosphates [(YPhO)(PhO)P(=O)Cl],[18a] a concerted mechanism with a late TS (in-line type TS I in Scheme 1) was proposed on the basis of large secondary inverse DKIEs, k_H/k_D = 0.61–0.87 (*vide infra*), and a large negative CIC, ρ_{XY} = −1.31. A concerted mechanism with the participation of a hydrogen bonded four-center-type TS II (Scheme 1) was proposed in Y-aryl phenyl chlorothiophosphates [(YPhO)(PhO)P(=S)Cl],[18c] Y-aryl ethyl chlorophosphates [(YPhO)(EtO)P(=O)Cl][18f] and Y-aryl ethyl chlorothiophosphates [(YPhO)(EtO)P(=S)Cl][18f] on the basis of primary DKIEs and negative CICs (k_H/k_D = 1.11–1.33 and ρ_{XY} = −0.22, k_H/k_D = 1.07–1.80 and ρ_{XY} = −0.60, and k_H/k_D = 1.06–1.27 and ρ_{XY} = −0.28, respectively). In dimethyl chlorothiophosphate [(MeO)$_2$P(=S)Cl],[18g] a linear free energy correlation and the DKIEs, k_H/k_D = 0.945–1.06 (greater value for stronger nucleophile), were rationalized by a gradual TS variation

from a backside nucleophilic attack (TS I) for weakly basic anilines to a frontside attack involving a hydrogen bonded four-center-type TS II for strongly basic anilines. In dimethyl chlorophosphate [(MeO)$_2$P(=O)Cl],[18g] diethyl chlorophosphate [(EtO)$_2$P(=O)Cl][18g] and dimethyl phosphinic chloride [Me$_2$P(=O)Cl][18i] the DKIEs are secondary inverse, k_H/k_D = 0.798–0.979, 0.714–0.919 and 0.703–0.899, respectively, implying a concerted mechanism dominantly through a TS I. In diethyl chlorothiophosphate [(EtO)$_2$P(=S)Cl][18g] and diphenyl thiophosphinic chloride [Ph$_2$P(=S)Cl],[18e] the DKIEs are relatively small primary normal, k_H/k_D = 1.01–1.10 and 1.00–1.10, respectively, implying a concerted mechanism through TS I and II. In diphenyl phosphinic chloride [Ph$_2$P(=O)Cl],[18d] methyl phenyl phosphinic chloride [MePhP(=O)Cl][18i] and Y-*S*-aryl phenyl phosphonochloridothioates [Ph(YPhS)P(=S)Cl],[h] the DKIEs are relatively large primary normal, k_H/k_D = 1.42–1.82, 1.62–2.10 and 1.15–1.59, respectively, implying a concerted mechanism predominantly through TS II. These results are summarized in Table 1 together with selectivity parameters (ρ_X, β_X, ρ_Y and ρ_{XY}), DKIEs involving deuterated anilines and proposed mechanisms.

We have also reported on the pyridinolysis of phosphate derivatives in MeCN.[19] In Y-aryl phenyl chlorophosphates,[19a] a concerted mechanism with an early TS (in-line type) was proposed on the basis of a linear free energy correlation and small negative CICs, ρ_{XY} = −0.15 and β_{XY} = −0.01.[20] However, in Z-aryl bis(4-methoxyphenyl) phosphates [(4-MeOPhO)$_2$P(=O)OPhZ],[19b] free energy correlations show biphasic concave downwards in the variation of the basicities of both nucleophiles and leaving groups. The CICs, ρ_{XZ}, and Brønsted coefficients, β_X (= β_{nuc}) and β_Z (= β_{lg}), showed that the mechanism (concerted or stepwise with rate-limiting formation of a TBP-5C intermediate) and attacking direction (backside or frontside) of pyridines are depending on both substituents in the nucleophiles (X) and leaving groups (Z). Furthermore, in Y-aryl phenyl isothiocyanophophates [(YPhO)(PhO)P(=O)NCS],[19c] the Hammett plots show biphasic concave downwards in the variation of the substituents in the substrates (Y), while concave upwards in the variation of the basicities of the nucleophiles. We proposed the mechanistic change at σ_Y = 0 from concerted to stepwise with rate-limiting expulsion
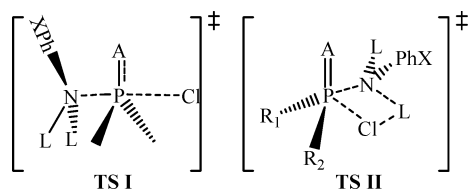
Scheme 1 Proposed TS structures (A = O or S; L = H or D).

of the leaving group from a TBP-5C intermediate. A frontside attack TS for more basic nucleophiles was proposed.

Herein, we report an examination of the DKIEs on the aminolysis of Y-O-aryl methyl phosphonochloridothioates with X-anilines in MeCN at 55.0 °C (Scheme 2) to clarify the phosphoryl transfer mechanism and to rationalize the substituent effects of the nucleophiles and substrates on DKIEs.
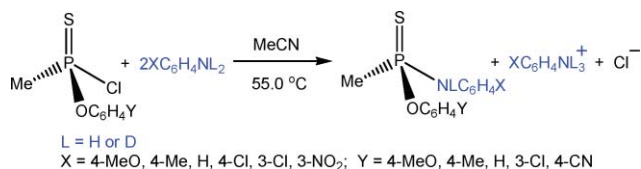
Scheme 2 Studied reaction systems.

Results and discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eqn (2) for all of the reactions under pseudo-first-order conditions with a large excess of aniline nucleophiles.

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

The k_0 values were negligible ($k_0 = 0$) in acetonitrile. The second-order rate constants (k_H and k_D) were obtained for at least five aniline concentrations ($[XC_6H_4NH_2(D_2)]$). The linear plots of eqn (2) suggest that there are no base-catalysis or noticeable side reactions and that the overall reaction is described by Scheme 2.

Second-order rate constants and selectivity parameters (ρ_X, β_X and ρ_Y) are summarized in Tables 2 and 3, respectively. The pK_a values of anilines in water are used to obtain the Brønsted β_X values and are justified experimentally and theoretically.[23] The pK_a and σ values of deuterated anilines are assumed to be the same as those of anilines. The rate increases with a more electron-withdrawing substituent (Y) in the substrate and with a more electron-donating substituent (X) in the nucleophile, consistent with a typical nucleophilic substitution reaction with negative charge development at the reaction center P atom and with positive charge development at the nucleophilic N atom in the TS.

It needs to be stressed that Hammett (Fig. S1†: $\log k_H$ vs. σ_X and $\log k_D$ vs. σ_X) and Brønsted (Fig. 1: $\log k_H$ vs. pK_{aX} and $\log k_D$ vs. pK_{aX}) plots are biphasic concave downwards with a "*discrete*" break region between X = H and 4-Cl in the variation of the nucleophiles. The biphasic concave downwards nonlinear

Table 2 Second-order rate constants ($k_{H(D)} \times 10^4/M^{-1}\,s^{-1}$) for the reactions of Y-O-aryl methyl phosphonochloridothioates with $XC_6H_4NH_2(D_2)$ in acetonitrile at 55.0 °C

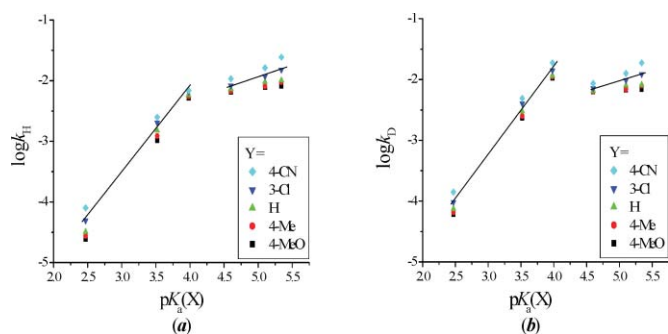| X \ Y		4-MeO	4-Me	H	3-Cl	4-CN
4-MeO	k_H	81.2 ± 1.8^a	94.1 ± 1.6	101 ± 2	152 ± 2	244 ± 4
	k_D	68.8 ± 1.1	78.9 ± 1.8	81.9 ± 1.4	122 ± 2	188 ± 2
4-Me	k_H	77.2 ± 1.4	80.2 ± 1.8	95.4 ± 2.8	118 ± 3	163 ± 2
	k_D	67.3 ± 0.9	68.6 ± 1.1	79.7 ± 1.3	97.5 ± 2.2	126 ± 2
H	k_H	64.4 ± 1.3	67.2 ± 1.5	72.5 ± 2.1	83.0 ± 1.5	108 ± 2
	k_D	62.4 ± 1.3	63.0 ± 1.5	64.9 ± 1.9	71.7 ± 1.4	85.9 ± 1.5
4-Cl	k_H	51.5 ± 0.3	55.0 ± 1.0	58.0 ± 1.2	65.2 ± 1.6	69.0 ± 1.3
	k_D	105 ± 2	111 ± 3	115 ± 1	141 ± 3	188 ± 3
3-Cl	k_H	10.3 ± 0.2	12.2 ± 0.3	15.0 ± 0.4	20.4 ± 0.4	25.0 ± 0.3
	k_D	23.2 ± 0.3	24.9 ± 0.4	29.8 ± 0.9	40.1 ± 0.6	49.0 ± 0.6
3-NO$_2$	k_H	0.242 ± 0.005	0.275 ± 0.007	0.322 ± 0.009	0.493 ± 0.009	0.800 ± 0.016
	k_D	0.605 ± 0.014	0.653 ± 0.014	0.750 ± 0.010	0.958 ± 0.024	1.41 ± 0.03

^{a} Standard deviation.

Table 3 Selectivity parameters^a (ρ_X, β_X and ρ_Y) for the reactions of Y-O-aryl methyl phosphonochloridothioates with $XC_6H_4NH_2(D_2)$ in acetonitrile at 55.0 °C

X	4-MeO	4-Me	H	4-Cl	3-Cl	3-NO$_2$
$-\rho_{Y(H)}{}^{b,c}$	0.49 ± 0.04^f	0.34 ± 0.02	0.23 ± 0.03	0.13 ± 0.01	0.40 ± 0.03	0.54 ± 0.03
$-\rho_{Y(D)}{}^{d,e}$	0.45 ± 0.04	0.29 ± 0.02	0.14 ± 0.02	0.26 ± 0.03	0.35 ± 0.01	0.38 ± 0.03

X = 4-MeO, 4-Me and H

Y	4-MeO	4-Me	H	3-Cl	4-CN
$-\rho_{X(H)}{}^g$	0.38 ± 0.06	0.52 ± 0.07	0.55 ± 0.12	0.97 ± 0.05	1.28 ± 0.18
$-\rho_{X(D)}{}^h$	0.16 ± 0.03	0.35 ± 0.10	0.39 ± 0.11	0.85 ± 0.05	1.23 ± 0.20
$\beta_{X(H)}{}^i$	0.14 ± 0.02	0.19 ± 0.03	0.20 ± 0.03	0.35 ± 0.04	0.46 ± 0.09
$\beta_{X(D)}{}^j$	0.06 ± 0.01	0.12 ± 0.04	0.14 ± 0.03	0.31 ± 0.03	0.44 ± 0.10

X = 4-Cl, 3-Cl and 3-NO$_2$

Y	4-MeO	4-Me	H	3-Cl	4-CN
$-\rho_{X(H)}{}^k$	4.84 ± 0.05	4.80 ± 0.04	4.74 ± 0.16	4.48 ± 0.26	4.10 ± 0.28
$-\rho_{X(D)}{}^l$	4.66 ± 0.01	4.65 ± 0.01	4.58 ± 0.12	4.56 ± 0.20	4.45 ± 0.08
$\beta_{X(H)}{}^m$	1.54 ± 0.01	1.53 ± 0.03	1.51 ± 0.07	1.43 ± 0.10	1.31 ± 0.11
$\beta_{X(D)}{}^n$	1.49 ± 0.02	1.48 ± 0.02	1.46 ± 0.06	1.45 ± 0.08	1.42 ± 0.05

^{a} The σ and pK_a values in water were taken from ref. 21 and 22, respectively. ^{b} Subscript (H) indicates that the value is calculated from k_H. ^{c} Correlation coefficients (r) were better than 0.980. ^{d} Subscript (D) indicates that the value is calculated from k_D. ^{e} r ≥ 0.965. ^{f} Standard deviation. ^{g} r ≥ 0.977. ^{h} r ≥ 0.959. ^{i} r ≥ 0.981. ^{j} r ≥ 0.943. ^{k} r ≥ 0.998. ^{l} r ≥ 0.999. ^{m} r ≥ 0.997. ^{n} r ≥ 0.998.

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Fig. 1 The Brønsted plots of $\log k_{H(D)}$ vs. $pK_a(X)$ for the reactions of Y-O-aryl methyl phosphonochloridothioates with $XC_6H_4NH_2$ (*a*) and $XC_6H_4ND_2$ (*b*) in acetonitrile at 55.0 °C.

Hammett and Brønsted plots with a "*continuous*" break region (curvature or break point) are thought to result from a change in the rate-limiting step from the breakdown to the formation of an intermediate, as the basicity of the nucleophile increases.[24] At low pK_a values of nucleophiles, the breakdown step (k_b) is rate-limiting with a steeper Brønsted slope. On the other hand, at high pK_a values of nucleophiles, the formation step (k_a) is rate-limiting with a smaller Brønsted slope. At the center of the Brønsted curvature, a nucleophile with $pK_a = pK_a°$ has the same leaving ability from the intermediate as that of the leaving group ($k_{-a} = k_b$). As a result, the Brønsted plot should be *continuous* with a break region or point. The *discrete* Brønsted plots are reported because of a desolvation step prior to the rate-limiting nucleophilic attack with a smaller value of β_X when the nucleophile is an anion and the solvent is polar protic, *e.g.*, water.[25] However, in the present work, the much smaller values of ρ_X and β_X for the more basic anilines are not ascribed to a desolvation step prior to the rate-limiting nucleophilic attack, since the aniline nucleophile is neutral and the MeCN solvent is dipolar aprotic. Thus, the "*discrete*" break region in the present work is not ascribed to a change in the rate-limiting step in a stepwise mechanism or to a desolvation step prior to a rate-limiting nucleophilic attack.

Table 4 reveals that the DKIEs are distinctly divided into two parts, secondary inverse ($k_H/k_D \ll 1$) for weakly basic anilines (X = 4-Cl, 3-Cl and 3-NO$_2$) and primary normal ($k_H/k_D > 1$) for strongly basic anilines (X = 4-MeO, 4-Me and H). The primary normal DKIE becomes systematically greater with a stronger nucleophile and with a more electron-withdrawing substituent in the substrate. As a result, the max. value of k_H/k_D is 1.30 when X = 4-MeO and Y = 4-CN while the min. value of k_H/k_D is 1.03 when X = H and Y = 4-MeO.
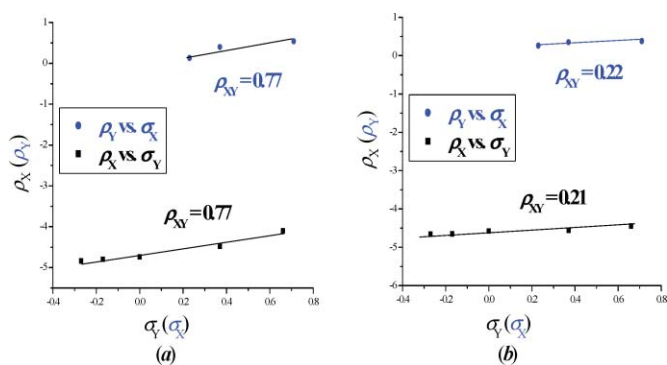
However, the tendencies of secondary inverse DKIEs are somewhat complicated and can be seen in two aspects: (a) substituent X in the nucleophile; (b) substituent Y in the substrate, respectively. Regarding (a), for X = 4-Cl, the k_H/k_D value becomes systematically greater with an electron-withdrawing substituent in the substrate, from Y = 4-MeO *via* 4-Me to H, and then systematically smaller with an electron-withdrawing substituent in the substrate, from Y = H *via* 3-Cl to 4-CN. For X = (3-Cl and 3-NO$_2$), the k_H/k_D value becomes systematically greater with a stronger nucleophile and with an electron-withdrawing substituent in the substrate. Regarding (b), for Y = (4-MeO, 4-Me and H), the k_H/k_D value becomes systematically smaller with a weaker nucleophile and with an electron-donating substituent in the substrate, resulting in the min. value of $k_H/k_D = 0.400$ when X = 3-NO$_2$ and Y = 4-MeO, and the max. value of $k_H/k_D = 0.504$ when X = 4-Cl and Y = H. For Y = (3-Cl and 4-CN), the k_H/k_D value becomes systematically smaller with a stronger nucleophile and with an electron-withdrawing substituent in the substrate, resulting in the min. value of $k_H/k_D = 0.367$ when X = 4-Cl and Y = 4-CN, and the max. value of $k_H/k_D = 0.567$ when X = 3-NO$_2$ and Y = 4-CN.

We propose the present trends as a mechanistic change from a stepwise mechanism with a rate-limiting leaving group departure from a TBP-5C intermediate involving a type TS I for weakly basic anilines (X = 4-Cl, 3-Cl and 3-NO$_2$) to a concerted mechanism involving a four-center hydrogen-bonded type TS II for strongly basic anilines (X = 4-MeO, 4-Me and H), based on the following grounds: (i) The magnitudes of ρ_X and β_X are much greater (even 30 times greater for ρ_X) for weaker nucleophiles ($\rho_X = -4.84$ to -4.10 and $\beta_X = 1.54–1.31$) than for stronger nucleophiles ($\rho_X = -1.28$ to -0.16 and $\beta_X = 0.46–0.14$) as shown in Table 2. It is well known that the magnitudes of ρ_X and β_X values for a stepwise reaction with a rate-limiting leaving group expulsion from the intermediate are greater than those of concerted mechanism. These are consistent with the proposed mechanism. (ii) The CICs for weaker nucleophiles are *positive* ($\rho_{XY(H)} = +0.77$ and $\rho_{XY(D)} = +0.21$: Fig. 2),[26] suggesting the stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate. While those for stronger nucleophiles are relatively large *negative* ($\rho_{XY(H)} = -0.95$ and $\rho_{XY(D)} = -1.11$: Fig. 3), suggesting a concerted mechanism.[15] (iii) The DKIEs for weaker nucleophiles are *extremely large* secondary inverse ($k_H/k_D = 0.367–0.567$; *unprecedently small* values), suggesting very severe steric crowding in the TS due to backside nucleophilic attack through in-line type TS I. While those for stronger nucleophiles are primary normal ($k_H/k_D = 1.03–1.30$), implying frontside nucleophilic attack through a hydrogen bonded
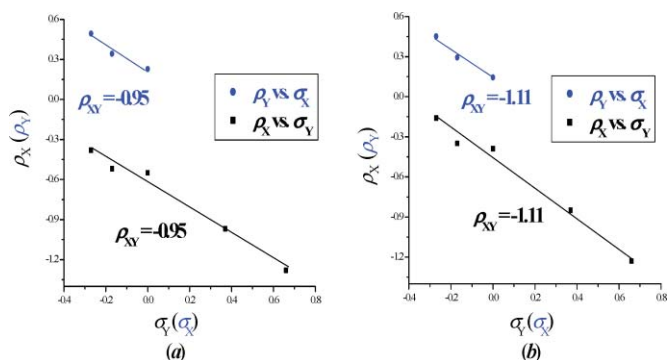
Table 4 Deuterium kinetic isotope effects (k_H/k_D) for the reactions of Y-O-aryl methyl phosphonochloridothioates with $XC_6H_4NH_2(D_2)$ in acetonitrile at 55.0 °C

X/Y	4-MeO	4-Me	H	3-Cl	4-CN
4-MeO	1.18 ± 0.03^a	1.19 ± 0.03	1.23 ± 0.04	1.25 ± 0.03	1.30 ± 0.03
4-Me	1.15 ± 0.03	1.17 ± 0.03	1.20 ± 0.04	1.21 ± 0.04	1.29 ± 0.03
H	1.03 ± 0.03	1.08 ± 0.03	1.12 ± 0.05	1.16 ± 0.03	1.26 ± 0.03
4-Cl	0.490 ± 0.011	0.495 ± 0.016	0.504 ± 0.011	0.462 ± 0.015	0.367 ± 0.009
3-Cl	0.444 ± 0.009	0.490 ± 0.014	0.503 ± 0.020	0.509 ± 0.013	0.510 ± 0.009
3-NO$_2$	0.400 ± 0.013	0.421 ± 0.014	0.429 ± 0.014	0.515 ± 0.016	0.567 ± 0.015

^{a} Standard error.

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Fig. 2 The ρ_{XY} ($= \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$) plots of ρ_X vs. σ_Y and ρ_Y vs. σ_X for the reactions of Y-O-aryl methyl phosphonochloridothioates with $XC_6H_4NH_2$ (a) and $XC_6H_4ND_2$ (b), when X = 4-Cl, 3-Cl and 3-NO$_2$ in acetonitrile at 55.0 °C. The obtained values by multiple regressions are $\rho_{XY(H)} = +0.77 \pm 0.17$ (r = 0.998) and $\rho_{XY(D)} = +0.21 \pm 0.11$ (r = 0.999).

Fig. 3 The ρ_{XY} plots of ρ_X vs. σ_Y and ρ_Y vs. σ_X for the reactions of Y-O-aryl methyl phosphonochloridothioates with $XC_6H_4NH_2$ (a) and $XC_6H_4ND_2$ (b), when X = 4-MeO, 4-Me and H in acetonitrile at 55.0 °C. The obtained values by multiple regressions are $\rho_{XY(H)} = -0.95 \pm 0.17$ (r = 0.980) and $\rho_{XY(D)} = -1.11 \pm 0.16$ (r = 0.976).

four-center type TS II. (iv) As shown in Fig. 1b, the fall-off rate, from X = H (weaker aniline nucleophile) to X = 4-Cl (stronger aniline nucleophile), strongly suggests that a frontside attack is more favorable than backside for stronger aniline nucleophiles.

Let us examine the proposed mechanism on the basis of the steric effects and DKIEs, and the substituent effects of the nucleophiles and substrates on DKIEs in the cases of weaker and stronger nucleophiles, separately.

Secondary inverse DKIEs for weaker nucleophiles (X = 4-Cl, 3-Cl and 3-NO$_2$)

We reported that the second-order rate constants (k_H with $C_6H_5NH_2$) for the anilinolysis of three phosphinates, $Me_2P(=O)Cl$,[18i] $MePhP(=O)Cl$[18i] and $Ph_2P(=O)Cl$[18d] gave relative rates of 4,520 ($k_H = 7.82$)[27]: 80 ($k_H = 0.138$): 1 ($k_H = 0.00173$ M^{-1} s^{-1}) in MeCN at 55.0 °C. Buncel and coworkers reported that the second-order rate constants for the ethanolysis of three phosphinates, $Me_2P(=O)(OPh-4-NO_2)$, $MePhP(=O)(OPh-4-NO_2)$ and $Ph_2P(=O)(OPh-4-NO_2)$ gave relative rates of 235 ($k_{EtO^-} = 230$): 69 ($k_{EtO^-} = 67.6$): 1 ($k_{EtO^-} = 0.980$ M^{-1} s^{-1}) in anhydrous ethanol at 25.0 °C.[28] Williams and coworkers reported that the second-order rate constants for the phosphate catalyzed
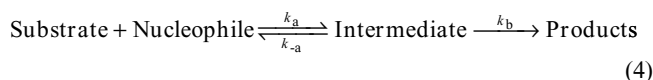
hydrolysis of two phosphinates, $Me_2P(=O)(OPh-4-NO_2)$ and $Ph_2P(=O)(OPh-4-NO_2)$ gave the relative rate of 52 ($k_{HPO_4^{2-}} = 1.06 \times 10^{-2}$): 1 ($k_{HPO_4^{2-}} = 2.05 \times 10^{-4}$ M^{-1} s^{-1}) in 10% dioxane–aqueous 0.1M NaCl at 25.0 °C.[29] These results are contrary to expectations for the electronic influence of the ligands: Ph ($\sigma_I = 0.12$) and Me ($\sigma_I = -0.01$) groups; Ph$_2$ ($\sum\sigma_I = 0.24$); MePh ($\sum\sigma_I = 0.11$); Me$_2$ ($\sum\sigma_I = -0.02$).[30] A plot of $\log k_H$ (for the unsubstituted aniline) against the Taft's steric constants according to eqn (3) for the anilinolysis of three phosphinates gives the sensitivity coefficient of the steric effects $\delta = 0.737$ (r = 0.999), 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)].[31] When the same values of $\sum E_S$ as in the anilinolysis of three phosphinates are used, $\delta = 0.478$ (r = 0.953: roughly linear) and $\delta = 0.345$ are obtained for the ethanolysis of three phosphinates and for the hydrolysis of two phosphinates, respectively. These results suggest that the phosphoryl transfer reaction rates are predominantly dependent on steric effects over the inductive effects of the ligands in the reaction series. The greater influence of steric effects is observed for anilinolysis than for ethanolysis (and hydrolysis), due to the larger size of the aniline nucleophile compared to the ethanol (and water) nucleophile.

$$\log k = \delta\sum E_S + C \qquad (3)$$

As mentioned earlier, the smallest value of the secondary inverse DKIE that we have ever obtained was $k_H/k_D = 0.61$ (*vide supra*) for the reaction of 4-chlorophenyl phenyl chlorophosphate with 4-chloroaniline.[18a] In Y-aryl 4-chlorophenyl chlorophosphates [(YPhO)(4-ClPhO)P(=O)Cl],[18b] a large secondary inverse DKIE, $k_H/k_D = 0.64$, was observed when X = 4-Cl and Y = 4-Me. These small values of secondary inverse DKIEs imply that steric hindrance plays an important role in the TS.

Comparing the DKIEs of P=S systems, $R_1R_2P(=S)Cl$, the values of $k_H/k_D(R_1,R_2)$ are as follows: 1.15–1.59 (YPhS,Ph)[18h] >1.10–1.46 (YPhO,4-ClPhO)[18c] >1.11–1.33 (YPhO,PhO)[18c] >1.06–1.27 (YPhO,EtO)[18f] >1.00–1.10 (Ph,Ph)[18e] ≈ 1.01–1.10 (EtO,EtO)[18g] >0.945–1.06 (MeO,MeO).[18g] The sequence of the k_H/k_D values shows that the DKIEs become greater as the sizes of the ligands become larger. Thus, backside nucleophilic attack becomes less favorable while frontside attack becomes more favorable as the sizes of the ligands become larger because of the increment of steric hindrance. In the present work, the two ligands of YPhO and Me, a subtle combination of large and small, resulted in two distinct pathways, frontside and backside attack for strongly basic and weakly basic anilines, respectively.

In the present work, the overall second-order rate constant can be given by $k_{H(D)} = (k_a/k_{-a})k_b = Kk_b$ in which the breakdown of the intermediate is the rate-limiting.

$$\text{Substrate} + \text{Nucleophile} \underset{k_{-a}}{\overset{k_a}{\rightleftarrows}} \text{Intermediate} \xrightarrow{k_b} \text{Products} \qquad (4)$$

Since the equilibrium step, K, results in an almost negligible DKIE due to the cancellation of the k_a and k_{-a} terms, the observed k_H/k_D reflects the leaving group expulsion rate constant, k_b, from the intermediate.[2f] As a result, the secondary normal β-type-DKIEs, $k_H/k_D > 1$, can be expected.[11–14,32,33] However, the observed DKIEs are secondary inverse, completely contrary to our

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expectations, and furthermore *extremely large secondary inverse*, $k_H/k_D = 0.367$–$0.567 << 1$.

The obtained secondary inverse DKIEs are mainly ascribed to a rate-limiting leaving group departure step, k_b. The observed *unprecedently small* k_H/k_D values should be accompanied with great extensive bond formation and severe steric congestion in the breakdown of the intermediate. Thus, the intermediate should be reactant-like and the TS2 should be very late and product-like (as shown in Scheme 3), resulting in $k_H/k_D = 0.367$–$0.567 << 1$ over the secondary normal β-type-DKIEs. The steric congestion is thus, very severe.
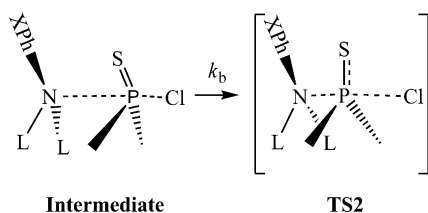
Scheme 3 Intermediate and TS 2 for the reactions of Y-*O*-aryl methyl phosphonochloridothioates with weakly basic anilines.

The sequence of k_H/k_D values depending on Y is almost in agreement with the expectations, Y = 4-MeO < 3-Cl < H < 4-Me < 4-CN (except X = 4-Cl), and $\partial\sigma_Y > 0$ leads to $\partial\rho_X > 0$ or $|\partial\rho_X| < 0$, *i.e.*, $\rho_{XY} > 0$. However, the observed sequence of k_H/k_D values depending on X is divided into two parts: X = 3-NO$_2$ < 3-Cl < 4-Cl for Y = (4-MeO, 4-Me, H), whereas X = 4-Cl < 3-Cl < 3-NO$_2$ for Y = (3-Cl, 4-CN). This implies that a weaker nucleophile approaches to a closer proximity to the reaction center for an electron-donating Y (min. $k_H/k_D = 0.400$ when X = 3-NO$_2$ and Y = 4-MeO), while a stronger nucleophile approaches a closer proximity to the reaction center for an electron-withdrawing Y (min. $k_H/k_D = 0.367$ when X = 4-Cl and Y = 4-CN).

Primary normal DKIEs for stronger nucleophiles (X = 4-MeO, 4-Me and H)

The observed primary normal DKIE may be proportional to the extent of hydrogen bond formation. A greater degree of deprotonation would occur with a greater extent of bond formation. Considering only the electrostatic interactions, greater deprotonation would occur when the substituent of the aniline has greater electron-withdrawing abilities and the substituent of the substrate has greater electron-donating abilities, resulting in the reverse of the obtained sequence. Thus, both the nucleophilicity of aniline and the electrophilicity of the substrate exceed the electrostatic term of the substituents to determine the degree of deprotonation in the present work. Thus, the stronger nucleophile ($\partial\sigma_X < 0$) leads to a greater extent of hydrogen bond formation ($\partial\rho_Y > 0$), *i.e.*, $\rho_{XY} < 0$, and the expected sequence of the k_H/k_D values is X = 4-MeO > 4-Me > H, consistent with the observed sequence. In the case of the substituent Y of the substrate, the extent of hydrogen bond formation would be greater ($\partial\rho_X < 0$ or $|\partial\rho_X| > 0$) when the electron-withdrawing ability of Y is greater ($\partial\sigma_Y > 0$), *i.e.*, $\rho_{XY} < 0$. The obtained sequence of k_H/k_D values, Y = 4-CN > 3-Cl > H > 4-Me > 4-MeO, is in line with the extent of bond formation. The reaction exhibited a large negative CICs, $\rho_{XY(H)} = -0.95$ and $\rho_{XY(D)} = -1.11$, suggesting that the degree of

bond formation is extensive in the TS. The TS is believed to involve a four-center hydrogen-bonded type TS II, the result of frontside attack. The four-center TS is seen to be more stable by forming a stronger hydrogen bond for a stronger nucleophile.

It should be noted that the real primary normal DKIE due to the hydrogen bond between the hydrogen of the N–H(D) moiety and the Cl leaving group is greater than the observed value, since the other hydrogen of the N–H(D) moiety yields the secondary inverse DKIE.

Experimental section

Materials

HPLC-grade MeCN was used for kinetic studies without further purification. Anilines were redistilled or recrystallized before use as previously described.[18] Deuterated anilines were prepared by heating anilines with D$_2$O at 85 °C for 72 h, with one drop of HCl added as a catalyst. After numerous attempts, the anilines were deuterated more than 98%, as confirmed by ^{1}H NMR.

Kinetic procedure

Pseudo-first-order rate constants (k_{obsd}) were measured conductometrically at 55.0 ± 0.1 °C and determined by curve fitting analysis in an origin program. The conductivity bridge was a self-made computer automated A/D converter one. [Y-*O*-aryl methyl phosphonochloridothioates] $\cong 3 \times 10^{-3}$ M and [X-C$_6$H$_4$NH$_2$(D$_2$)] = 0.1–0.5 M were employed. The $k_{H(D)}$ values are the averages of more than three runs and reproducible to within ±3%.

Conclusions

The kinetics and mechanism of the reactions of Y-*O*-aryl methyl phosphonochloridothioates with substituted X-anilines and deuterated X-anilines are investigated in MeCN at 55.0 °C. In the case of weakly basic anilines, DKIEs are unusually large secondary inverse and the sign of CICs is positive. On the contrary, in the case of strongly basic anilines, DKIEs are primary normal and the sign of CICs is negative. A stepwise mechanism with a rate-limiting leaving group departure from the intermediate, through backside nucleophilic attack in-line-type TS I, is proposed for weakly basic anilines, while a concerted mechanism through a hydrogen bonded, four-center-type TS II is proposed for strongly basic anilines. We know that free energy correlation of biphasic concave downwards could be ascribed to the change of the reaction mechanism from stepwise to concerted as the basicity of the nucleophile increases. We have found that the secondary inverse DKIE could be as small as or equal to, 0.4.

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