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Kinetic Isotope Effect; A Physical Organic Tool to Interpret Reaction Mechanism

Review Article

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***Abstract*— Phosphoryl transfer reactions are important because of analogy to the numerous enzyme-catalyzed reactions at phosphorus. The kinetics and mechanism of the aminolyses of $R_1R_2P(=S)Cl$, 1 type substrates in MeCN were investigated by means of the deuterium kinetic isotope effects (DKIEs) involving deuterated anilines ($XC_6H_4ND_2$) and deuterated pyridine (C_5D_5N) and compared on the basis of DKIEs and steric effects of the two ligands (R_1 = $-C_6H_5$ and R_2 = $-O-C_6H_4Y$). The primary DKIEs suggests that partial deprotonation of pyridine occurs by hydrogen bonding in the rate-determining step as occurring in the pyridinolysis of 1 [(k_H/k_D)net = 1.28-1.35, > 1]. In case of anilinolysis The DKIEs were distinctly divided into two parts, unprecedented great secondary inverse (k_H/k_D = 0.439- 0.918 << 1) for the strongly basic aniline and primary normal (k_H/k_D = 1.05-1.34) for the weakly basic anilines, rationalized by a gradual TS variation from backside to frontside nucleophilic attack. The trigonal bipyramidal pentacoordinate TS is proposed for a backside attack, while a hydrogen-bonded, four-center-type TS for a frontside attack.**

***Keywords*— Phosphoryl transfer reactions, aminolyses, deuterium kinetic isotope effects (DKIEs),TS Structure,**

I. INTRODUCTION

The measurement of the Deuterium Kinetic Isotope Effects (DKIEs) has found widespread use in mechanistic study of various reactions as KIEs are one of the few experimental probes for the TS of the rate limiting step of a reaction [1]. DKIEs of atoms at different positions within a molecule can provide details of the TS structures. It is also very insightful and convenient tool for studies of reaction mechanisms. DKIEs is a kinetic method that can in principal tells about bonding changes in the rate limiting step of a reaction as the rate of reaction varies when an atom is replaced by a different (usually heavier atom) [2]. Isotopic substitution does not affect the PES of the molecule nor does it perturb the electronic energy levels. It is only those properties that are dependent upon atomic masses which are affected; for chemical purposes, the perturbation can be considered to be limited to vibrational frequencies [3].

Each atom in a molecule may move in three dimensions and for a molecule containing *N* atoms one might consider 3*N* independent modes of motion. However, six of these modes involve motion of the molecules as a whole (three for translation and three for rotation) and so are not vibrations. There are, then, (3*N*-6) normal vibrational modes present, each one associated with vibrational energy (part of the internal energy, *U*). Moreover, each vibrational frequency, and hence energy, depends on the masses of the atoms vibrating and will vary with the isotopic species. Vibrational energy will usually change during the course of a reaction or between reagent and transition state since some bonds are in the course of a reaction or between reagent and transition state since some bonds are in the course of being broken or made and their associated frequencies will be affected. Isotopic substitution should therefore affect reaction rates.

The extent to which this occurs depends greatly upon the relative masses of the isotopes, and the mass of D doubles to that of H (greatest) so hydrogen isotope effects are the most thoroughly examined, the following discussion will refer to this case, rate constants being denoted, k_H, k_D, but the same principles apply to any pair of isotopes. If $k_H \neq k_D$ a kinetic isotope effect (KIE) exists, expressed as the ratio, k_H/k_D; it is described as 'normal', if, $k_H/k_D > 1$ and 'inverse', if, $k_H/k_D < 1$ [2, 3].
The following types of isotope effect are distinguished:

(a) Primary kinetic isotope effect (PKIE): in which the bond to the isotopic atom is broken in the rate determining step,

$$k_H/k_D >> 1$$

(b) Secondary kinetic isotope effect (SKIE), in which the bond to the isotopic atom (s) remains intact throughout the reaction,

$$k_H/k_D << 1 \text{ or } k_H/k_D, \text{ around, } 1$$

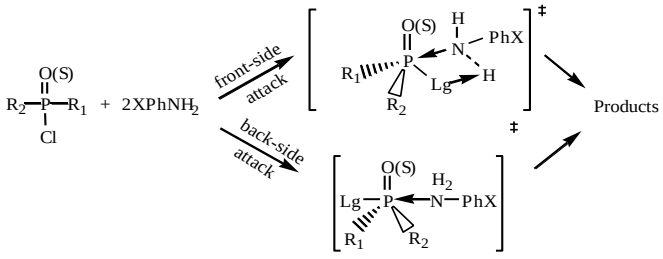
(c) Solvent isotopic effects, which result from isotopic differences in the medium, e.g., if the solvent is

changed from H_2O to D_2O, then $k_{(H2O)}$ / $k_{(D2O)}$ is obtained as solvent isotope effect.

Two principal factors influence the magnitude of DKIEs [4].
(i) The temperature-independent factor (TIF); connected with the mass difference of isotopic species and the effect of this difference on frequency of crossing the energy barrier (TS) along the reaction coordinate favoring light isotopic species reacting faster than their 'heavy' isotopomers.
(ii) The temperature-dependent factor (TDF); reflects changes in bonding around the isotopic atom. This factor is larger than unity when bonds to the isotopic atom is weaker in TS than in reactant and smaller than unity for the opposite situation. Overall the PKIEs are greater than unity when a bond is being broken to the isotopic atom because both factors are larger than unity. Conversely when a bond is being made to the isotopic atom the PKIEs are small or inverse due to the partial cancellation of the two factors. An isotope effect of approximately unity may mean that the isotope sensitive step is not rate determining or else that the step is rate determining.

Phosphoryl transfer reactions play a fundamental role in a wide range of biological processes including basic metabolism, energy transduction, gene expression, and cell signaling [5]. There is continuous interest in phosphoryl transfer and related reactions for their importance in environment as well as biological process [6].

In previous work, this lab reported upon various types of phosphoryl and thiophosphoryl transfer reactions: anilinolyses [7], pyridinolyses [8] and theoretical studies [9]. The kinetics and mechanism of the anilinolyses of $R_1R_2P(=O$ or $=S)Cl$ type substrates in MeCN were investigated by means of DKIEs selectivity parameters (Hammett coefficients ρ_X, ρ_Y, Bronsted coefficient β_X and cross interaction constant ρ_{XY}), as well as steric effects of the two ligands (R_1 and R_2). A considerable amount of work has been focused on the two types of phosphoryl transfer reaction mechanisms, stepwise ($A_N + D_N$) through a trigonal bipyramidal pentacoordinate (TBP-5C) intermediate, and concerted (A_ND_N) through a single pentacoordinate transition state (TS) [10]. The attacking direction of the nucleophile can be backside and/or frontside, depending on the substrate, nucleophile, leaving group, and reaction condition [11, 12].



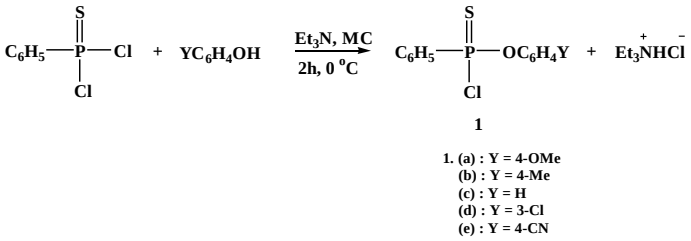
Scheme 1 *Schematic representation of nucleophilic attack on P centre in concerted mechanism.*

The kinetics and mechanism of the aminolyses of Y-O-aryl phenyl phosphonochloridothioates, $R_1R_2P(=S)Cl$, 1 type substrates in MeCN were investigated by means of the deuterium kinetic isotope effects (DKIEs) involving deuterated anilines ($XC_6H_4ND_2$) [13] and deuterated pyridine (C_5D_5N) [14] and compared on the basis of DKIEs and steric effects of the two ligands (R_1 = $-C_6H_5$ and R_2 = $-O-C_6H_4Y$) to interprete the dramatic mechanistic changes occurring due to the change in substituents.

II. RESEARCH METHOD

A. Material

GR grade Phenylthiophosphonic dichloride, substituted anilines and pyridines, substitued phenols, substitued thiophenols, triethylamine, deuterated pyridine (C_5D_5N; 99 atom% D), D_2O were purchased and used in this work without further purification except amines. Amines were generally recrystallized or distilled if necessary for further purification before use [13, 14]. The substrates, *O*-Aryl phenyl phoshonochloridothioates were prepared as mentioned "*Scheme 2*". HPLC grade acetonitrile was used for the kinetic studies without further purification. Deuterated anilines were prepared by heating anilines with D_2O at 85 ^oC 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 ^1H NMR.



Scheme 2 *Synthetic route for the preparation of the substrates:1 (a) – (e)*

B. Characterization: 1(a) – 1(e)

***O* – (4 – Methoxyphenyl) phenyl phosphono chloride thioate, 1(a):**
White solid; mp 48–50 °C; ^1H NMR, (400 MHz, $CDCl_3$) δ_H 8.15 (dd, J = 16.7, 7.0 Hz, 2H), 7.68 – 7.62 (m, 1H), 7.59 – 7.54 (m, 2H), 7.26 – 7.21 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H, OCH_3,); ^{13}C NMR, (100 MHz, $CDCl_3$) δ_C 157.4 (d, J = 2.2 Hz), 143.1 (d, J = 11.3 Hz), 135.1 (d, J_{P-C} = 140.2 Hz), 133.3 (d, J = 3.8 Hz), 130.7 (d, J = 12.9 Hz), 128.5 (d, J = 16.7 Hz), 122.5 (d, J = 5.3 Hz), 114.5 (d, J = 1.5 Hz), 55.6 (s, OCH_3); ^{31}P NMR, (162 MHz, $CDCl_3$) δ_P 91.4 (s, 1P); IR (KBr, cm^{-1}) 3062 (C–H, aromatic), 2952 ($-CH_3$ Asym), 2839 ($-CH_3$ Sym), 1503 (C=C, Ar), 1441 (P-C, Ar), 1252, 1183, (P-O-C_6H_4), 832 (P=S);GCMS: m/z, 298 (M^+); Anal. Calcd for $C_{13}H_{12}O_2PSCl$: C, 52.27; H, 4.05; S, 10.73. Found: C, 52.35; H, 4.11; S, 10.87

O **– (4 – Methylphenyl) Phenyl Phosphono chloridothioate, 1(b):**
Colorless liquid; ^{1}H NMR, (400 MHz, $CDCl_3$) δ_H 8.15 (dd, *J* = 17.2, 7.2 Hz, 2H), 7.66–7.60 (m, 1H), 7.57–7.52 (m, 2H), 7.26 – 7.14 (m, 4H), 2.36 (s, 3H, CH_3,); ^{13}C NMR, (100 MHz, $CDCl_3$) δ_C 147.4 (d, *J* = 12.1 Hz), 135.7 (d, *J* = 2.3 Hz), 135.1 (d, J_{P-C} = 140.2 Hz), 133.2 (d, *J* = 3.8 Hz), 130.6 (d, *J* = 12.8 Hz), 130.1 (d, *J* = 2.3 Hz), 128.5 (d, *J* = 16.7 Hz), 121.2 (d, *J* = 5.3 Hz), 20.8 (s, CH_3); ^{31}P NMR, (162 MHz,$CDCl_3$) δ_P 90.7 (s, 1P); IR (neat, cm^{-1}) 3056 (C–H, aromatic), 2920 (–CH_3 Asym), 2858 (–CH_3 Sym), 1503 (C=C, Ar), 1439 (P–C, Ar), 1385, 1191 (P–O–C_6H_4), 821 (P=S); GCMS: m/z, 282 (M^+); Anal. Calcd for $C_{13}H_{12}OPSCl$: C, 55.23; H, 4.28; S, 11.34, Found: C, 55.42; H, 4.38; S, 11.24

O **– Phenylphenylphosphonochloridothioate, 1(c):**
Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (dd, *J* = 16.6, 7.4 Hz, 2H), 7.68 –7.60 (m, 1H), 7.57–7.52 (m, 2H), 7.41– 7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 149.8 (d, *J* = 11.4 Hz), 135.2 (d, J_{P-C} = 140.3 Hz), 133.4 (d, *J* = 2.2 Hz), 130.7 (d, *J* = 12.8 Hz), 129.6 (s), 128.6 (d, *J* = 16.7 Hz), 126.1 (s), 121.6 (d, *J* = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 90.3 (s, 1P); Colorless liquid; IR (neat, cm^{-1}) 3061 (C–H, Ar), 1494 (C=C, Ar), 1444 (P–C, Ar), 1196, 1124, (P–O–C_6H_4), 791 (P=S); GCMS: m/z, 268 (M^+); Anal. Calcd for $C_{12}H_{10}OPSCl$: C, 53.64; H, 3.75; S, 11.93, Found: C, 53.85; H, 3.91; S, 11.83

O **– (3 – Chlorophenyl) phenylphosphonochlorido thioate, 1(d) :**
Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (dd, *J* = 16.6, 6.0 Hz, 2H), 7.65–7.62 (m, 1H), 7.58–7.52 (m, 2H), 7.33–7.29 (m, 2H), 7.25–7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 149.9 (d, *J* = 11.4 Hz), 134.8 (d, *J* = 2.3 Hz), 134.7 (d, J_{P-C} = 140.3 Hz), 133.5 (d, *J* = 3.8 Hz), 130.6 (d, *J* = 12.9 Hz), 130.2 (d, *J* = 1.5 Hz), 128.6 (d, *J* = 16.6 Hz), 126.3 (d, *J* = 2.3 Hz), 122.2 (d, *J* = 5.3 Hz), 120.0 (d, *J* = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 90.5 (s, 1P); IR (neat, cm^{-1}) 3063 (C–H, aromatic), 1585 (C=C, Ar), 1474 (P–C, Ar), 1198, 1112, (P–O–C_6H_4), 865 (P=S); GCMS: m/z, 302 (M^+); Anal. Calcd for $C_{12}H_9OPSCl_2$: C, 47.54; H, 2.99; S, 10.58, Found: C, 47.61; H, 3.08; S, 10.61

O **– (4 – Cyanophenyl phenylphosphonochlorido thioate, 1(e):**
White solid; mp, 100–102°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.14 (dd, *J* = 16.2, 7.9 Hz, 2H),7.72 (d, *J* = 8.8 Hz, 2H), 7.69-7.67 (m, 1H), 7.62-7.57 (m, 2H), 7.44 (dd, *J* = 7.8, 3.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 152.7 (d, *J* = 11.4 Hz), 134.3 (d, J_{P-C} = 140.3 Hz), 133.82-133.72 (3 peaks for 2C), 130.6 (d, *J* = 14.4Hz), 128.7 (d, *J* = 17.5 Hz), 122.7 (d, *J* = 5.3 Hz), 117.9 (d, *J* = 1.5 Hz) 110.0 (C≡N); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 90.3 (s, 1P); IR (KBr, cm^{-1}) 3090 (C–H, aromatic), 2232 (C≡N),1493 (C=C, Ar), 1439 (P–C, Ar), 1202, 1165, 1115 (P–O–C_6H_4), 850, (P=S); GCMS: m/z, 293 (M^+); Anal. Calcd for $C_{13}H_9ONPSCl$: C, 53.15; H, 3.09; S, 10.92, N, 4.77. Found: C, 52.74; H, 3.09; S, 11.44, N, 4.51.

C. Product Analysis (Anilinolysis) [13]

O – (4 – Methoxyphenyl)phenylphosphonochlorido thioate was treated with excess 4 – methylaniline for more than 15 half-lives at 55.0 °C in acetonitrile and the product was isolated maintaining other necessary steps.
[(4 – CH_3O – C_6H_4O)(C_6H_5)P(=S)(NHC_6H_4 – 4 – CH_3)]: Reddish brown gelatinous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 14.3, 7.4 Hz, 2H), 7.51 – 7.44 (m, 3H),7.10 (dd, *J* = 6.9, 3.3 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.84 – 6.78 (m, 4H), 5.68 (d, *J* = 8.8 Hz, 1H, N – H), 3.76 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 56.8 (d, *J* = 2.3 Hz), 143.5 (d, *J* = 9.9 Hz), 137.1 (d, *J* = 3.8 Hz), 133.3 (d, J_{P-C} = 146.3 Hz), 131.9 (d, *J* = 3.8 Hz), 131.6 (s), 130.7 (d, *J* = 11.4 Hz), 129.7 (s), 128.6 (d, *J* = 15.1 Hz), 122.6 (d, *J* = 3.7 Hz), 118.0 (d, *J* = 6.8 Hz), 114.4 (d, *J* = 1.5 Hz), 55.5 (s, OCH_3), 20.6 (s, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 73.43 (s, 1P); IR (KBr, cm^{-1}) 3251 (– NH –), 3000 (C–H, aromatic), 1503 (C=C, Ar) 1440 (P–C, Ar), 1373, 1193 (P–O–C_6H_4), 832 (P=S); GC-MS: m/z 369 (M^+); Anal. Calcd for $C_{20}H_{20}O_2NPS$: C, 65.02; H, 5.46; S, 8.68, N, 3.79. Found: C, 65.09; H, 5.60; S, 8.81, N, 3.65.

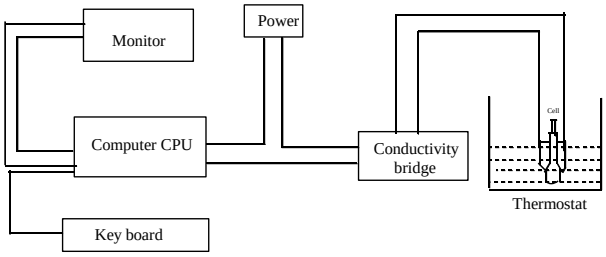
D. Product Analysis (Pyridinolysis) [14]

O – Phenyl phenylphosphonochloridothioate, 1(c) was treated with excess 3 – acetylpyridine for more than 15 half-lives at 35.0 °C in acetonitrile and the product was isolated maintaining other necessary steps.
$O(NC_5H_4)P(=S)(OC_6H_5)(C_6H_5)]^+Cl^-$: Yellow gummy substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.28 (s, 1H), 8.86 (d, *J* = 5.2Hz, 1H), 8.45 (d, *J* = 7.6Hz, 1H), 8.07 (dd, *J* = 14.4, 7.6 Hz, 2H), 7.62 – 7.61 (m, 1H), 7.50 – 7.42 (m, 3H), 7.24 – 7.05 (m, 5H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 194.0 (–C=O, 1C), 151.3 (d, *J* = 10.0 Hz), 148.2, 145.2, 140.4, 135.9 (d, J_{P-C}= 149.0 Hz), 133.7, 131.6 (d, *J* = 14.0 Hz), 130.9 (d, *J* = 12.2 Hz), 129.2 (d, *J* = 27.3 Hz), 128.1 (d, *J* = 22.4 Hz), 125.7, 124.4 (d, *J* = 2.5 Hz), 122.0 (d, *J* = 3.8 Hz), 26.0 (CH_3, 1C, s); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 81.7 (1P, s); IR (KBr, cm^{-1}) 3064 (C–H, aromatic), 2930, 2867 (–CH_3), 1704 (C=O), 1491, 1442 (P–C, Ar), 1210, 1136, (P–O–C_6H_4), 714 (P=S); HRMS-EI m/z, M^+ Calcd. for positive ion, $C_{19}H_{17}O_2PSN^+$: 354.0718, Found: 354.0730

E. Kinetics

The kinetic study was performed with a computer controlled conductivity bridge “Scheme 3”, equipped with a constant temperature circulating bath (*LAUDA, E200, Germany*) to keep the reaction mixture at 55.0 ± 0.2 °C for aninilinolysis [13] and 35.0 ± 0.2 °C for pyridinolysis [14]. All the reactions were carried out under pseudo first order conditions in which amine

concentrations were at least 20 times greater than the substrate concentration. Thus the pseudo first order rate (k_{obsd}) was obtained experimentally which will ultimately produce second order rate constant (k_2).



Scheme 3 *Schematic diagram for conductometric instrumental set up for kinetic studies.*

After completion of the reaction the stored data was treated for the determination of k_{obsd} in ORIGIN (Version 7.0) program from conductivity, λ (μS cm^{-1}) *vs*. time (s) nonlinear curve fitting plot based on Guggenheim method "equation (1)" and shown in *"Fig. 1".*

$$\lambda_t = \lambda_\infty - (\lambda_\infty - \lambda_0)\, e^{(-k_{obsd} \times t)} \qquad (1)$$

Second-order rate constants, k_2 were reckoned from the slope of the plots of k_{obsd} vs [Nu], "equation (2)", which gave very good linearity in all cases. For these plots at least five different amine concentrations were employed and replicate values of k_{obsd} were determined to obtain the second-order rate constants (k_2) reproducible to within ± 3%. Finally the average k_2 has been chosen from several determinations (at least two).

$$k_{obsd} = k_0 + k_2\,[Nu] \qquad (2)$$

Similarly deuterated aniline and pyridine were treated to obtain k_2, values for deuterium effect. In this study k_H is expressed as average of second order rate constants with pyridine and k_D indicates average of second order rate constant with deuterated amines.

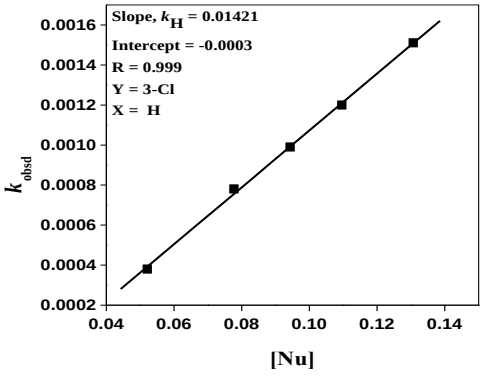


Fig. 2 *A plot of k_{obsd} vs. [pyridine] for [(3 – ClPhO)(Ph)P(=S)Cl + C_5H_5N] in acetonitrile at 35.0 °C*

where, λ_0 = initial conductivity value
λ_t = conductivity value at any time and
λ_∞ = conductivity value at infinity

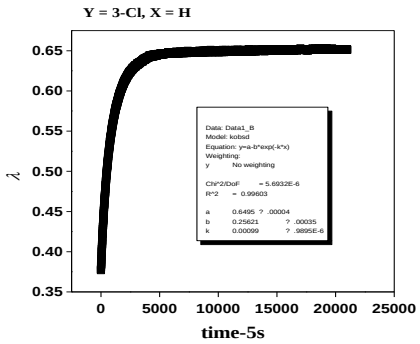


Fig. 1. *A plot of conductivity (λ) vs. time (interval 5s) for the reaction [(3-ClPhO)(Ph)P(=S)Cl + C_5H_5N] in acetonitrile at 35.0 °C.*

III. RESULTS AND DISCUSSION

The observed DKIEs, k_H/k_D, of the pyridinolysis of 1a- 1e involving *d*-5 pyridine (C_5D_5N) are summarized in TABLE 1. The observed k_H/k_D values are greater than unity (1.05–1.11). The experimental DKIES was modified and précised by Perrin and his coworkers as they reported that the basicities of *β*-deuterated analogs of benzylamine, *N*, *N*-dimethylaniline and methylamine increase roughly 0.02 pK_a units per deuterium and these effects are additive [15]. For five deuterium atoms in *d*-5 pyridine this gives an expected ΔpK_a of approximately +0.1 unit. For Y = H in **1c**, considering the β_X value of 0.88 [14] shown in "equation (3)",

$$\log(k_H/k_D)_{expd} = -(\beta_X \times \Delta pK_a) \qquad (3)$$
$$-(0.88 \times 0.1) = -0.088$$
$$\text{expected } (k_H/k_D)_{expd} = 0.82$$

and the expected k_D value of *d*-5 pyridine is $(k_D)_{expd} = k_H/0.82 = 11.2 \times 10^{-3}/0.82 = 13.7 \times 10^{-3}$. However, the observed $(k_D)_{obsd}$ value of *d*-5 pyridine is 10.1×10^{-3} and $(k_H/k_D)_{obsd}$ is 1.11. Thus, the *net* KIE excluding the increased pK_a effect of *d*-5 pyridine for Y = H in **1c** can be expressed as "equation (4)".

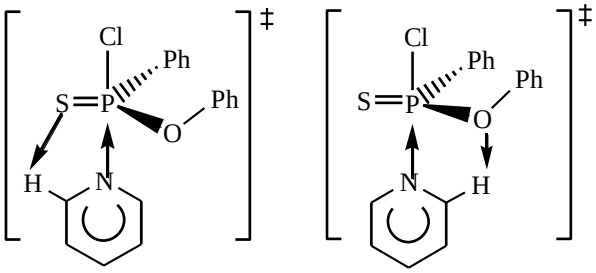
$$(k_H/k_D)_{net} = (k_H/k_D)_{obsd}/(k_H/k_D)_{expd} = 1.11/0.82 = 1.35 \quad (4)$$

TABLE 1. DKIES FOR THE REACTIONS OF *O* – ARYL PHENYLPHOSPHONOCHLORIDOTHIOATES WITH *D*-5 PYRIDINE (C_5D_5N) IN ACETONITRILE AT 35.0 °C

Y	k_H (× 10^3/$M^{-1}s^{-1}$)	k_D (× 10^3/$M^{-1}s^{-1}$)	$(k_H/k_D)_{obsd}$	$(k_H/k_D)_{expd}$	$(k_H/k_D)_{expd}$ / $(k_H/k_D)_{obsd}$ [b]
4-MeO	9.28 ± 0.05	8.50 ± 0.07	1.09 ± 0.01[a]	0.82	1.33
4-Me	10.4 ± 0.09	9.88 ± 0.17	1.05 ± 0.02	0.82	1.28
H	11.2 ± 0.2	10.1 ± 0.1	1.11 ± 0.02	0.82	1.35
3-Cl	14.4 ± 0.2	13.6 ± 0.1	1.06 ± 0.02	0.81	1.31
4-CN	17.5 ± 0.1	16.5 ± 0.1	1.06 ± 0.01	0.80	1.33

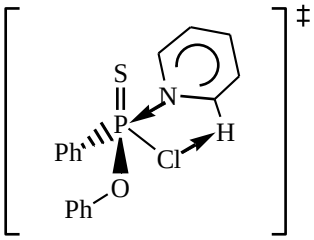
[a]Standard error {= $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$}, [16] [b]*Net kinetic isotope effect.*

The $(k_H/k_D)_{net}$ value of **1** (1.28-1.35, see "TABLE 1") and are greater than unity. The *net* KIE of greater than unity, $(k_H/k_D)_{net}$ > 1, implies a primary KIE [17]. The primary KIE suggests that partial deprotonation of pyridine occurs by hydrogen bonding in the rate-determining step as occurring in the pyridinolysis of **1** [$(k_H/k_D)_{net}$ = 1.28-1.35]. The experimental DKIEs also shows primary KIE [$(k_H/k_D)_{obsd}$ = 1.05-1.11]. Thus, we can suggest possible TS structures of the pyridinolysis of **1 (TS 1a, TS 1b, TS 1c)**, as follows:



TS 1a

TS 1b



TS 1c

Fig. 3 *Some plausible TS structures for the pyridinolysis of 1 (TS 1a, TS 1b, TS 1c**),***

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Considering less electronegativity of the sulfur of P=S, a hydrogen bond between sulfur of P=S atom and hydrogen (deuterium) atom in the C−H(D) moiety in **TS 1a** would not be that favorable but cannot be fully neglected. The structure of **TS !c** is in line with the frontside nucleophilic attack which we have proposed in a earlier paper. We can suggest that the primary KIE, is attributed to the hydrogen bond between the leaving group Cl and the hydrogen (deuterium) atom in the C−H(D). However at this point, **TS 1b** can be neglected till further systematic work of P=S system will clearly elucidate the reaction mechanism.

The nucleophilic substitution reactions of Y-O-aryl phenyl phosphonochloridothioates with $XC_6H_4NH_2(D_2)$ in MeCN at 55.0 ^oC are kinetically investigated. Surprising substituent effects of X and Y on DKIEs (k_H/k_D) are observed. The DKIEs systematically increase from extremely large secondary inverse (k_H/k_D = 0.439) to primary normal (k_H/k_D =1.34) as both substituents of the nucleophile and substrate change from electron-donating to electron-withdrawing,It can be rationalized by a gradual TS variation from backside to frontside nucleophilic attack. The trigonal bipyramidal pentacoordinate TS is proposed for a backside attack, while a hydrogen-bonded, four-center-type TS for a frontside a hydrogen-bonded, four-center-type TS for a frontside attack.

The DKIEs (k_H/k_D) for anilinolysis are summarized in TABLE 2. However, the substituent effects of X and/or Y on the DKIEs do not show the same trends as in the present work; the DKIEs showed trends invariably increase from an extremely large secondary inverse (k_H/k_D < 1, 0.439; min when X = Y = 4-MeO) to a primary normal (k_H/k_D > 1, 1.34; max when X = 3-Cl and Y = 4-CN). As both substituents of the nucleophile (X) and substrate (Y) change from electron-donating to electron-withdrawing k_H/k_D invariably increasing.

The primary normal DKIEs became systematically greater with a weaker nucleophile (X = H, 4-Cl, 3-Cl) and with a more electron-withdrawing substituent in the substrate (Y = 4-MeO-4-CN). In the case of secondary inverse DKIEs, the variation trends are in consistency.

TABLE 2. DEUTERIUM KINETIC ISOTOPE EFFECTS (KH/KD) OF THE REACTIONS OF $(YC_6H_4O)PHP(=S)CL$ WITH $XC_6H_4NH_2(D_2)$ IN MECN AT 55.0 ^{O}C

X/Y	4-MeO	4-Me	H	3-Cl	4-CN
4-MeO	0.439±0.01[a]	0.464±0.01	0.532± 0.02	0.672±0.02	0.675± 0.016
4-Me	0.852± 0.03	0.864± 0.01	0.883± 0.02	0.906± 0.01	0.918 ± 0.01
H	1.03 ± 0.03	1.05 ± 0.02	1.11 ± 0.01	1.11 ± 0.04	1.14± 0.01
4-Cl	1.05 ± 0.01	1.07 ± 0.03	1.13 ± 0.04	1.14 ± 0.01	1.16± 0.05
3-Cl	1.06 ± 0.03	1.08 ± 0.02	1.14 ± 0.02	1.29 ± 0.04	1.34± 0.01

Standard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ [16]

In the present work, the DKIEs suggest that the nucleophile attacks the substrate from both the backside (type TSb) and frontside (type TSf) line-type. TSb would be predominant for a stronger nucleophile and a more electron-donating Y substituent in the substrate. When X = Y = 4-MeO, the steric congestion in the TS is so severe that the secondary inverse DKIE could be as small as 0.439. As X and Y change from electron-donating to electron-withdrawing, the DKIEs gradually increase.These results suggest that the fraction of backside attack gradually decreases, while that of frontside attack gradually increases. When both X and Y are electron-withdrawing groups (X = 3-Cl and Y = 4-CN) frontside attack (a hydrogen-bonded, four-center-type TSf) would be predominant and, as a result, primary normal DKIE is as large as 1.34.

Alternatively, the experimental results can be divided simply into two parts depending only on nucleophiles, and suggest the mechanism as follows:

(i) predominant backside attack with a secondary inverse k_H/k_D = 0.439-0.918 for strongly basic anilines (X = 4-MeO and 4-Me); (ii) predominant frontside attack with a primary normal k_H/k_D = 1.03-1.34 for weakly basic anilines (X = H, 4-Cl, and 3-Cl). present work, it may be more reasonable that the fraction of backside and frontside attacks of the aniline nucleophile changes gradually with variation in the substituents of X and Y.

It is worthy of note that another plausible TS structure

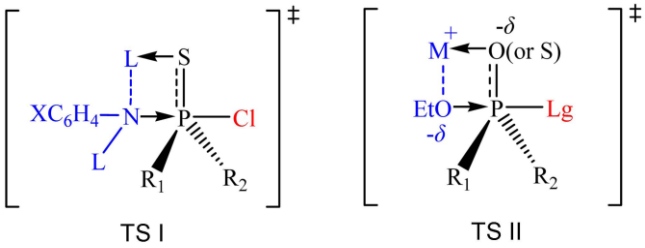

Fig. 4 *Plausible TS structure for anilinolysis*

It is worthy of note that another plausible TS structure with k_H/k_D > 1 could be TS I in Scheme 3, taking into account a four-membered TS II in the ethanolyses of the phosphinates, paraxon, and parathion with alkali metal ions by Buncel [18] and Um [19]. However, positive charge development on the hydrogen (deuterium) atom of the N–H(D) moiety in the TS I would be much smaller than that on M+ ions, so that a hydrogen bond involving the acceptor P=S, as in the TS I, is not feasible. Most of all, the obtained DKIEs of k_H/k_D = 0.439-1.34 cannot be rationalized by the TS I. Thus, the TS I can be safely ruled out to substantiate the observed primary normal DKIEs of k_H/k_D > 1 TS structure.

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