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EFFECT OF SUBSTITUENTS ON REACTIVITY AND REACTION MECHANISM OBSERVED IN S_N REACTION OF SOME ORGANOPHOSPHORUS COMPOUNDS: BASED ON PHYSICAL ORGANIC METHODOLOGIES

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Abstract

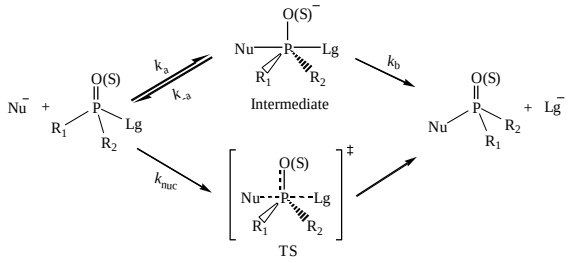
The aminolyses of tetracoordinated organophosphorus compounds were investigated by varying substituents around phosphorus center or in nucleophile. The reactivity is expressed in terms of second-order rate constant, k_2 and measured conductometrically. Physical organic chemistry tools; Hammett (ρ), Brönsted (β) LFER, CICs and heavy atom KIE have been used in quest for the mechanistic information. The pyridinolysis of *O*-aryl phenyl phosphonochloridothioates [PhP(=S)(OPh-Y)Cl, 1, and *O,O*-diphenyl Z-*S*-phenyl phosphorothiolates [$(PhO)_2P(=O)(S\text{-}Ph\text{-}Z)$], 2, in acetonitrile at 35.0 ^oC, were observed by varying substituents around phosphorus centre (Y in 1, Z in 2) or in nucleophile (X) and extended to pyridinolysis of 4-Chlorophenyl phenyl Chlorophosphate [4–ClPhOP(=O)(OPh)Cl], 3, in acetonitrile at 5.0 ^oC (present study). The variation in X and Y in system 1 shows LFER with negative value of the Hammett coefficients, ρ_X, –(4.35 ~ 4.75), CICs, $\rho_{XY} = -0.46$, which is in favour of concerted S_N2 mechanism. The LFER plots obtained for 2 with the variation in X, with negative value of the ρ_X, –(4.43 ~ 4.76) indicating same mechanism as the system 1, substituent (Z) variations (log k_2 *vs.* Z) are biphasic concave downwards with breaks at Z = H, ρ_{XZ} = −0.70 for Z = electron donating group, ρ_{XZ} = + 0.76 for Z = electron withdrawing group interpreting as the change in mechanism at Z = H from concerted to stepwise. In the light of the above reported results the LFER obtained for 3 with negative value of the ρ_X , –5.66 can be interpreted as S_N2 process, with greater extent of bond formation in TS than that of 1, 2.

Key Words: Organophosphorus compounds, pyridinolysis, reactivity, Hammett (ρ), CICs, KIE, TS structure

Introduction

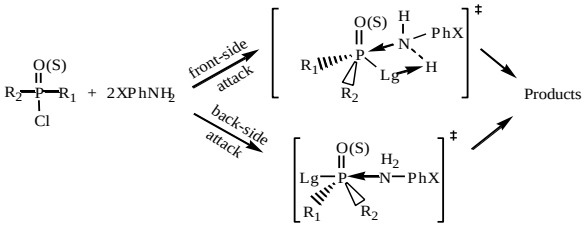
Phosphoryl transfer and related reactions are ubiquitous in environment as well as biological chemistry with many opportunities for research or applications development especially due to its relevance to biological chemistry as well as its usefulness as agricultural chemicals like pesticides, oil and gasoline additives, etc. (Lumbiny 2009). Despite many researches that have been carried out there are still many facets of the aminolyses of organophosphorus and their thio analogues compounds that are not well understood. A series of kinetics and mechanism of nucleophilic substitution reactions on phosphoryl group (P=O) and thiophosphoryl group (P=S) have been reported earlier (Guha *et al*. 2000, Lee *et al*. 2000, Hoque *et al.* 2007, Lumbiny *et al*. 2008, Adhikary *et*

al. 2011). The above studies are relied on Physical organic chemistry methods. Hammett and Brönsted linear free energy relationship (LFER), cross interaction constants (CICs), heavy atom kinetic isotope effects (KIE), activation enthalpy and activation entropy have provided unambiguous evidence for the interpretation of the mechanistic pathway. It has been reported that nucleophilic substitution at a (thio)phosphoryl (P=S/O) center generally proceeds either through stepwise mechanism with a trigonal bipyramidal pentacoordinated (TBP-5C) intermediate (upper route) or an S_N2 mechanism with TBP-5C transition state (TS) (lower route), Scheme 1. (Skoog and Jencks 1984, Thatcher and Kluger 1989, Hosfield *et al.* 1999, Guha *et al*. 2000, Lee *et al*. 2000, Williams 2000, Chapados *et al*. 2001, Harger 2002, Hengge 2002, 2005, Humphry *et al.* 2004**,** Swamy and Kumar 2006, Um and Kumar. 2006, Hoque *et al.* 2007, Adhikary *et al*. 2008, Lumbiny *et al*. 2008, Adhikary *et al*. 2011)



Scheme 1. Schematic representation on nucloephilic substitution at P centre on (P=S/O) group transfer reaction.

Our very recent studies showed that in case of concerted mechanism the nucleophile can approach towards reaction centre in two different ways. A hydrogen-bonded, four-center type TS is suggested for a frontside attack while the TBP-5C TS is suggested for a back-side attack based on the deuterium kinetic isotope effects. as shown in Scheme 2 (Guha and Kumar. 2000, Lee *et al*. 2000, Hoque *et al*. 2007, Lumbiny *et al*. 2008, Adhikary *et al*. 2011).



Scheme 2. Schematic representation of nucleophilic attack on P centre in concerted mechanism.

This is also very strongly claimed from previous studies as the substituents around the P centre varies in leaving or nonleaving group, the reactivity, selectivity, finally mechanistic pathway for S_N reaction varies a lot. The variation can be rationalized from our recent investigation on the pyridinolysis of *O*-aryl phenyl phosphonochloridothioates

[PhP(=S)(OPh-Y)Cl, 1**,** and *O*,*O*-diphenyl Z-*S*-phenyl phosphorothiolates [$(PhO)_2$ P(=O)(S-Ph-Z)], 2 in acetonitrile at 35.0 ^oC, being observed by varying substituents around P centre (Y in 1, Z in 2) or in nucleophile (X). The reported mechanism according to LFER is S_N2 without any change in mechanism for the system 1, but for 2 a change in mechanism is interpreted at Z = H from concerted to stepwise with rate-limiting expulsion of the leaving group(Lumbiny *et al*. 2008, Adhikary *et al*. 2011).

To gain further evidence in support of the above mechanism, the aminolyses of 4-Chlorophenyl phenyl Chlorophosphate [4–ClPhOP(=O)(OPh)Cl], 3**,** with tertiary amine, substituted pyridines have been carried out at 5.0 ^oC in acetonitrile (present study). It is also very instructive to compare the behavior of 3, [4–ClPhOP(=O)(OPh)Cl], with that of 1, [PhP(=S)(OPhY)Cl] and 2, [$(PhO)_2$P(=O)(SPhZ)] comparing the reactivities, the selectivity parameters, and the magnitudes of the CICs with those obtained in our previous studies to assess their influence on TS and the reaction mechanism as well.

Materials and Methods

GR grade starting materials, substitued pyridines, deuterated pyridine (C_5D_5N; 99 atom% D) were purchased and used. HPLC grade acetonitrile (less than 0.005% H_2O content) were used to prepare nucleophile solution to study kinetics (Guha *et al*. 2000, Lee *et al*. 2000, Hoque *et al*. 2007, Lumbiny *et al*. 2008, Adhikary *et al*. 2011).

Kinetics (Guha *et al*. 2000, Lee *et al*. 2000, Hoque *et al*. 2007, Lumbiny *et al*. 2008, Adhikary *et al*. 2011): The kinetic study was performed with a computer controlled conductivity bridge, equipped with a constant temperature circulating bath to keep the reaction mixture at 35.0 ± 0.2 ^oC (for 1, 2), 5.0 ± 0.2 ^oC (for 3). 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 by using Guggenheim equation (equation 1), and nonlinear curve fitting method in ORIGIN program,

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

[where, λ_0 = initial conductivity, λ_t = conductivity at any time, λ_∞ = conductivity at infinity]

which will ultimately produce second-order rate constant (k_2) from the slope of the plots of k_{obsd} vs [Nu], in 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%.

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

Similarly deuterated 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 pyridine.

Theory : Free Energy Relationship (Issacs 1995, Willams 2003). The mechanism of a chemical reaction can be interpreted using LFER; an empirical observations which can be derived when the shapes of the potential energy surfaces (PES) of a reaction are not substantially altered by varying the substituent (Willams 2003).

Hammett Equation (Hansch *et al.* 1991, Issacs 1995, Pross 1995, Mihai *et al.* 2003, Willams 2003): Hammett's success is in treating the electronic effect of substituents on the rate of equilibria of organic reactions, can be expressed as follows equation 3(a) and 3(b)

$$\log (k_X/k_H) = \sigma\rho....[3(a)] \quad \text{or} \quad \log (K_X/K_H) = \sigma\rho...[3(b)]$$

applied to the influence of *m*- or *p*-substituents X on the reactivity of the functional group Y in the benzene derivative *m*- or *p*-XC_6H_4Y. k_X or K_X is the rate or equilibrium constant, respectively, for the given reaction of *m*- or *p*-XC_6H_4COOH(4), k_H or K_H refers to the reaction of C_6H_5COOH, i.e., X = H, σ is the substituent constant, ρ is the reaction constant.

Significance of Sign and Magnitude of ρ: the susceptibility of the reaction to substituents, (+ve) value; a reaction favored by EWS, (–ve) value; reverse. (a) $\rho = 1$, for benzoic acid (4) ionization. (b) $\rho > 1$, the reaction is more sensitive to substituents than (4) and negative charge is built during the reaction. (c) $0 < \rho < 1$, less sensitive to substituents than (4) and negative charge is built. (d) $\rho = 0$, no sensitivity to substituents, and no charge is built. (e) $\rho < 0$, the reaction builds positive charge.

The Brönsted equation (Zuman and Patel 1984): The Gibbs free energy for proton dissociation is proportional to the activation energy (equation 4a, 4b) for the catalytic step. When the relationship is not linear, the chosen group of catalysts do not operate through the same reaction mechanism.

$$k_b = G_b K_b^{\beta} = G_b (K_W/K_a)^{\beta} = G_b K_a^{-\beta} \qquad (4a)$$

$$\log k_b = \beta pK_a + \text{constant} \qquad (4b)$$

The Brönsted correlation of rate constants with nucleophile pK_a (β_X) is one measure of the degree of nucleophile bond formation in the rate determining TS. Reactions that have low values for proportionality constants (β_X) are considered to have a transition state closely resembling the reactant with little proton transfer, with a high value, resembles product .

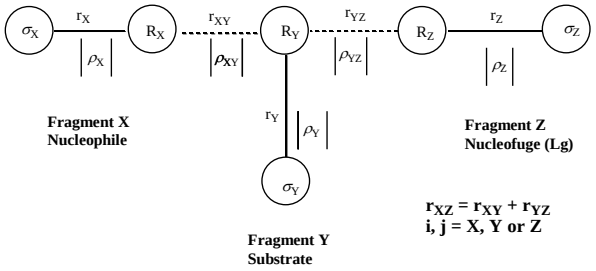
Cross-Interaction Constant Theory (Miller 1959, Cordes and Jencks 1962, Jencks and Jencks 1977, Dubois *et al.* 1984, Jencks 1985, Lee 1990, 1992, 1995, Lee and Lee 1999, Williams 2000, Lee and Lee 2001,).

Definition: The multiple substituents effect can also be analyzed quantitatively by extending these classical equations to include second derivative parameter, termed as Cross-interaction constants (CICs), shown in equation 5a and 5b. The CICs, ρ_{ij} (Hammett type constant) and β_{ij} (Brönsted type constant) represent the intensity of interaction

between the two interacting molecules i (e.g., a nucleophile) and j (an electrophile) in the adduct (Scheme 3)

$$\log (k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \ldots (5a)$$

$$\log (k_{ij}/k_{HH}) = \beta_i \Delta pK_i + \beta_j \Delta pK_j + \beta_{ij} \Delta pK_i \Delta pK_j \ldots (5b)$$



Scheme 3. Typical S_N2 TS. . (Lee 1990, 1992, 1995, Lee and Lee 1999, Williams 2000, Lee and Lee 2001).

Table 1. Summarization of significance of the sign and magnitude of the CICs in explaining quantitative mechanistic criteria.

Mechanism	Sign
S_N1	$\rho_{XY} = 0$, $\rho_{YZ} > 0$, $\rho_{XZ} = 0$
Concerted S_N2	$\rho_{XY} < 0$, $\rho_{YZ} > 0$, $\rho_{XZ}^{>} < 0$
Addition-Elimination	
formation of $T^{\pm}$	$\rho_{XY} < 0$, $\rho_{YZ} \equiv 0$, $\rho_{XZ}^{>} < 0$
breakdown of $T^{\pm}$	$\rho_{XY} > 0$, $\rho_{YZ} < 0$, $\rho_{XZ} > 0$

Kinetic Isotope Effects (Paneth and O'Leary 1991, Issacs 1995, Olaf *et al*. 1995, Carrol 1998)

The measurement of the KIEs tells about bonding changes in the rate limiting step of a reaction as the rate of reaction varies when an atom is replaced by an isotope (usually comparison of H with D, k_H/k_D); provide details of the TS structures. The following types of isotope effect are distinguished:

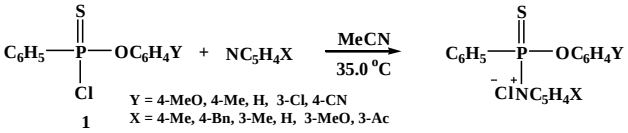
(a) Primary kinetic isotope effect (PKIE): in which the bond is broken in the rate determining step, favors front side nucleophilic attack.; $k_H/k_D >> 1$.

(b) Secondary kinetic isotope effect (SKIE), in which the bond to the isotopic atom (s) remains intact throughout the reaction, $k_H/k_D << 1$ or k_H/k_D, around, 1; favors back side nucleophilic attack.

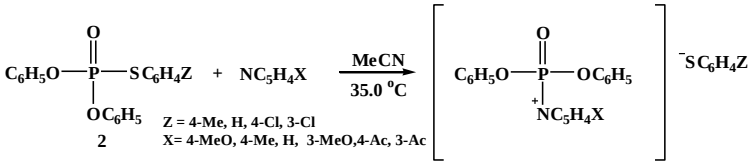
(c) Solvent isotopic effects, which result from isotopic differences in the medium, e.g., if the solvent is changed from H_2O to D_2O, then $k_{(H2O)} / k_{(D2O)}$ is obtained as solvent isotope effect.

Results and Discussion

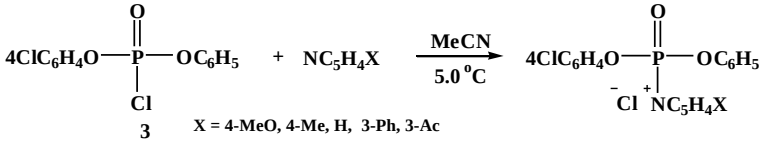
All the reactions in this study pyridinolysis of 1, 2 in acetonitrile at 35.0 ºC (Schemes 4 and 5) and 3, in acetonitrile at 5.0 ºC (Scheme 6) follow pseudo first-order kinetics. The second-order rate constants, (k_2), obtained from pseudo first-order rate constants (k_{obsd}), are summarized in Tables 2, 3 and 4 respectively together with the selectivity parameters, Hammett (ρ_X, ρ_Y), Brönsted (β_X) coefficients and CIC's (ρ_{XY}).



Scheme 4. Reaction systems for the pyridinolysis of 1, in acetonitrile at 35.0 °C.



Scheme 5. Reaction systems for the pyridinolysis of 2, in acetonitrile at 35.0 °C.



Scheme 6. Reaction systems for the pyridinolysis of 3, in acetonitrile at 5.0 °C (present study).

Table 2. k_2 (× 10^3/M^{-1} s^{-1}) and selectivity parameters[a] for the pyridinolysis of compounds 1.

X\Y	4-MeO	4-Me	H	3-Cl	4-CN	ρ_Y[d]
4-Me	85.5	99.6	106	152.0	195.0	0.38
4-Bn	40.6	43.2	46.8	61.9	80.6	0.32
3-Me	24.7	25.7	27.5	36.8	47.8	0.31
H	9.28	10.4	11.2	14.4	17.5	0.29
3-MeO	3.82	4.31	4.64	5.77	6.57	0.24
3-Ac	0.33	0.35	0.36	0.39	0.43	0.11
$-\rho_X$[b]	4.35	4.39	4.40	4.62	4.75	ρ_{XY}[e] =
β_X[c]	0.87	0.88	0.88	0.93	0.95	−0.46

[a] σ (Hansch *et al*. 1991) and pK_a (Albert and Serjeant 1984), [b] Correlation coefficients, r, were better than 0.994. [cd] r ≥ 0.988. [e] r = 0.990.

Table 3. k_2 (× 10^3/M^{-1} s^{-1}) and selectivity parameters for the pyridinolysis of compounds 2.

X\Z	4-Me	H	4-Cl	3-Cl	ρ_Z[d]	ρ_Z[e,f]
4-MeO	590.0	1090	513.0	467.0	1.57	–1.04
4-Me	183.0	284.0	77.8	68.3	1.12	–1.75
H	28.3	44.2	11.0	8.70	1.14	–1.98
3-MeO	17.5	34.8	5.89	3.85	1.76	–2.66
4-Ac	2.63	3.42	2.08	1.60	0.67	–0.90
3-Ac	0.24	0.37	0.23	0.20	1.	–0.75
$-\rho_X$[b]	4.64	4.76	4.43	4.51	ρ_{XZ}[d,g]= –0.70	ρ_{XZ}[d,h] = +0.76
β_X[c]	0.93	0.95	0.88	0.89		

[a] σ (Hansch *et al*. 1991) and pK_a (Albert and Serjeant 1984), [b]Correlation coefficients, r, were better than 0.974. [c]r ≥ 0.963 [d]Z = 4-Me and H. [e]Z = H, 4-Cl, and 3-Cl. [f]r ≥ 0.955. [g]r = 0.956. [h]r = 0.951.

Table 4. k_2 (× 10^2/M^{-1} s^{-1}) and selectivity parameters[a] for the pyridinolysis of compounds 3.

X	4-MeO	4-Me	H	3-Ph	3-Ac	$-\rho_X$	β_X[c]
4-Me	121	27.8	3.16	0.918	0. 026	5.66	1.14

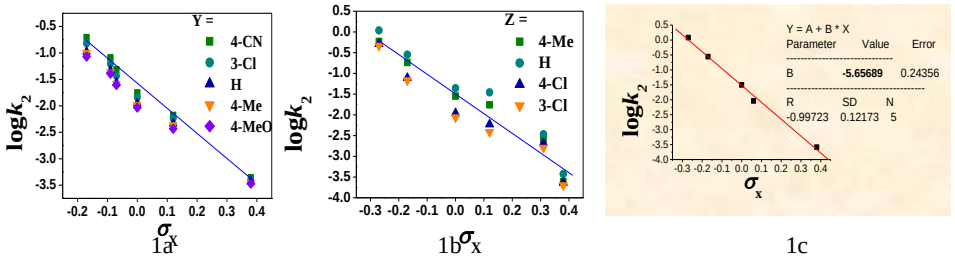
[a] σ (Hansch *et al*. 1991) and pK_a (Albert and Serjeant 1984) [b]Correlation coefficients, r, were better than 0.997. [c]r = 0.997

The second-order rate constants (k_2 × 10^3/$M^{-1}s^{-1}$) of the pyridinolysis 1 with Y = H: (PhO)PhP(=S)Cl, 2 with Y = H: $(PhO)_2P(=O)SPh$, 3: (4–ClPhO)PhOP(=O)Cl obey the following order of reactivity respectively (Tables 2 - 4)

2 (44.2) > 3 (31.6) > 1 (11.2)

At a glance, the reaction rates seem to be proportional to the positive charge on reaction center P. However, it is well known that P=O substrates are more reactive than P=S because of electronegativity difference between O and S, favoring O over S (Gregersen *et al.* 2003, Hengge 2005).

The Hammett plots for substituent (X) variations in the nucleophile (log k_2 vs. σ_X, Fig. 1) and Bronsted plots (log k_2 vs. pK_a(X), Fig. 3) show linearity for 1, 2, 3, suggesting no change in mechanism. It differs from 2 for the Hammett plots for substituent (Z) variations in the leaving group (log k_2 vs. σ_Z) are biphasic concave downwards with breaks at Z = H as shown in Fig. 2 is interpreted as the change in mechanism with variation in Z.



1a 1b 1c

Fig. 1. The Hammett plots for the determination of ρ_X for the reactions of 1 (1a), 2(1b), 3(1c).

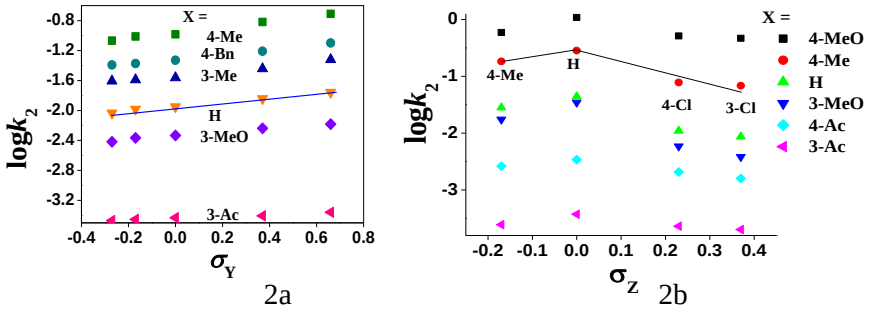


Fig. 2. The Hammett plots for the determination of ρ_Y for the reactions of 1 (2a), 2(2b).

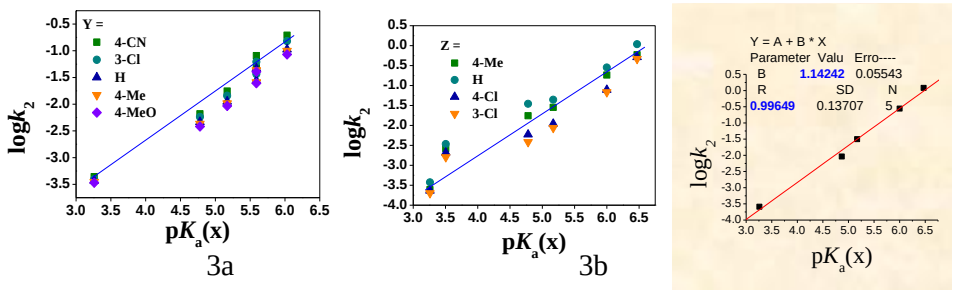


Fig. 3. The Brönsted plots for the determination of β_X for the reactions 1 (3a), 2(3b), 3(3c).

The selectivity parameters, the negative CIC's, ρ_{XY} (–0.46, Table 2) of 1 implies that the reaction proceeds through a concerted S_N2 mechanism. The sign of CIC's for 2, reversal of ρ_{XZ} from positive in $\sigma_Z \leq 0$ (ρ_{XZ} = –0.70) to negative in $\sigma_Z \geq 0$ (ρ_{XZ} = +0.76) may indicate the mechanism change from concerted to stepwise with rate-limiting expulsion of the leaving group. The obtained ρ_X = –4.35 to –4.75, and β_X = 0.87 to 0.95, of 1, ρ_X (= –4.43 to –4.76) and β_X (= 0.88-0.95) in the present work, 2, are somewhat smaller than those in 3**,** ρ_X = –5.66, and β_X = 1.14. The comparable ρ_X and β_X of 3 with those of 1, 2 indicates concerted mechanism for 3, with a later TS i.e., a greater extent of bond-formation than that of 1 as well as 2.

The observed k_H/k_D values of 1 are greater than unity (1.05-1.11, for 1, 1.06 for 3, Table 5) implies the primary KIE favors front side nucleohilic attack in TS. The larger magnitude of selectivity parameters also observed for this.

Table 5. Deuterium kinetic isotope effects (k_H/k_D) for the reactions of 1 and 3 with *d*-5 pyridine(C_5D_5N) in acetonitrile at 35.0 °C and 5.0 °C respectively.

Y	4-MeO	4-Me	H	3-Cl	4-CN
Y(1) k_H (× 10^3/M^{-1} s^{-1})	9.28 ± 0.05	10.4 ± 0.09	11.2 ± 0.2	14.4 ± 0.2	17.5 ± 0.1
Y(1) k_D (× 10^3/M^{-1} s^{-1})	8.50 ± 0.07	9.88 ± 0.17	10.1 ± 0.1	13.6 ± 0.1	16.5 ± 0.1
Y(3) k_H (× 10^3/M^{-1} s^{-1})			31.6 ± 0.2		
Y(3) k_D (× 10^3/M^{-1} s^{-1})			30.6 ± 0.1		
1,$(k_H/k_D)_{obsd}$	1.09 ± 0.01[a]	1.05 ± 0.02	1.11 ± 0.02	1.06 ± 0.02	1.06 ± 0.01
3,$(k_H/k_D)_{obsd}$			1. 04 ± 0.08		

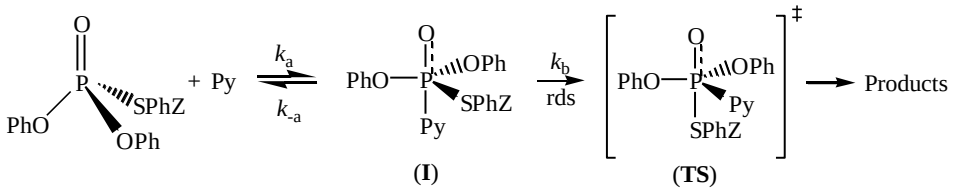
[a]Standard error {= $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$} (Crumpler and Yoh 1940).

We can suggest possible TS structures of the pyridinolysis of 1 (TS 1a), 3 (TS 1b), in Fig. 4, as these structure are in line with the frontside nucleophilic attack which we have proposed in a earlier paper (Guha *et al*. 2000, Lee *et al*. 2000, Hoque *et al*. 2007, Lumbiny *et al*. 2008, Adhikary *et al*. 2011) and with the primary KIE, due to the hydrogen bond between the leaving group Cl and the H(D) atom in the C−H(D).

TS 1a **TS 1b**

Fig. 4. The TS structure for 1 (1a), 3(1b).

In the case of the frontside nucleophile attack [ap(Nu)-eq(Lg)] is observed rather than eq(Nu)-ap(Lg) in a TBP-5C intermediate. Since pyridine is less bulky than PhO and/or ZPhS it can undergo an intramolecular ligand exchange process by Berry-type pseudorotation (or turnstile rotation) and thus [eq(Nu)-ap(Lg)] can be observed in the TS (Scheme 7).



(**I**) (**TS**)

Scheme 7. Schematic representation for Berry-type pseudorotation (or turnstile rotation) for the present system.

Finally it can be concluded that according to the reported mechanism is S_N2 without any change in mechanism for the system 1, but for 2 a change in mechanism is interpreted at Z = H from concerted to stepwise with rate-limiting expulsion of the leaving group. In the light of the system 1, 2 the pyridinolysis of 3 with ρ_X, −5.66 should proceed through S_N2 indicating no change in mechanism with greater extent of bond formation in TS than that of 1, 2 having TS structure 1b.

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