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Kinetics and Mechanism of the Pyridinolysis of Diethyl Thiophosphinic Chloride in Acetonitrile

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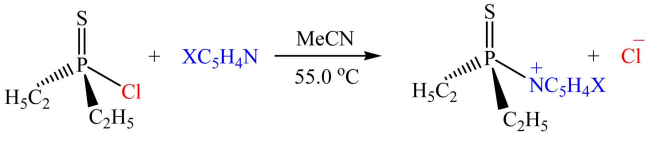
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Phosphoryl and thiophosphoryl transfer reactions have been studied extensively by this lab: pyridinolysis,[1] anilinolysis,[2] benzylaminolysis,[3] and theoretical study.[4] In the present work, the nucleophilic substitution reactions of diethyl thiophosphinic chloride [**3:** $Et_2P(=S)Cl$] with substituted X-pyridines (XC_5H_4N) are investigated kinetically in acetonitrile at 55.0 ± 0.1 °C to gain further information into the thiophosphoryl transfer reaction mechanism (Scheme 1). The pyridinolyses of eight $R_1R_2P(=S)Cl$-type substrates in MeCN are reviewed to obtain systematic information on the thiophosphoryl transfer reaction mechanism. The kinetic results are discussed on the basis of the steric effects of R_1 and R_2, electrophilicity of the substrate on reactivity of the substrate, cross-interaction constants (ρ_{XY}), and substituent effects of the nucleophiles (X) and substrates (Y) on the pyridinolysis mechanism. The eight $R_1R_2P(=S)Cl$-type substrates employed are as follows: dimethyl thiophosphinic chloride [**1:** $Me_2P(=S)Cl$];[1h] dimethyl chlorothiophosphate [**2:** $(MeO)_2P(=S)Cl$];[1g] diethyl thiophosphinic chloride (**3:** present work); diethyl chlorothiophosphate [**4:** $(EtO)_2P(=S)Cl$];[1g] Y-*O*-aryl methyl phosphonochloridothioates [**5:** $Me(YC_6H_4O)P(=S)Cl$];[1k] diphenyl thiophosphinic chloride [**6:** $Ph_2P(=S)Cl$];[1d] Y-*O*-aryl phenyl phosphonochloridothioates [**7:** $Ph(YC_6H_4O)P(=S)Cl$];[1f] and Y-aryl phenyl chlorothiophosphates [**8:** $(PhO)(YC_6H_4O)P(=S)Cl$].[1j] The numbering of the substrates (**1-8**) follows the sequence of the size of the two ligands, R_1 and R_2.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq. (1) for all of the reactions under pseudo-first-order conditions with a large excess of pyridine nucleophile. The k_0 values were negligible ($k_0 = 0$) in MeCN.



X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN

Scheme 1. The studied reaction system.

The second-order rate constants (k_2) were determined for at least five concentrations of pyridines. The linear plots of eq. (1) suggest that there is no base-catalysis or noticeable side reactions and that the overall reaction is described by Scheme 1.

$$k_{obsd} = k_0 + k_2 [XC_5H_4N] \quad (1)$$

The k_2 values are summarized in Table 1. The substituent effects of the nucleophiles upon the pyridinolysis rates correlate well with those for a typical nucleophilic substitution reaction with negative ρ_X and positive β_X values.[5] The Brönsted β_X coefficient was obtained by correlating log k_2(MeCN) with $pK_a(H_2O)$,[5] which was justified theoretically and experimentally.[6] Both the Hammett (Fig. 1; log k_2 *vs* σ_X) and Brönsted [Fig. 2; log k_2 *vs* pK_a(X)] plots, however, are biphasic concave upwards with a break point at X = 3-Ph. The magnitudes of ρ_X (= −4.47 ± 0.04) and β_X (= 0.92 ± 0.04) values with more basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph) are greater than those (ρ_X = −1.91 ± 0.06 and β_X = 0.34 ± 0.05) with less basic pyridines (X = 3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

Table 2 shows the second-order rate constants (k_2) with unsubstituted pyridine at 35.0 °C, natural bond order (NBO) charges on the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],[2e,7] Brönsted coefficients (β_X), and cross-interaction constants (CICs; ρ_{XY})[8] for the pyridinolyses of eight $R_1R_2P(=S)Cl$-type substrates in MeCN. The arrangement of the substrates in the column follows the sequence of the degree of steric hindrance (i.e., bulkiness) of the two ligands. In general, the values of β_X with more basic pyridines are greater than those with less basic pyridines except **5**. Comparison the second-order rate constant of the pyridinolysis (C_5H_5N) of **3** with the value of its P=O counterpart [$Et_2P(=O)Cl$], the rate ratio of $k_2[Et_2P(=O)Cl]/k_2[Et_2P(=S)Cl] = 127 \times 10^{-3}/0.0960 \times 10^{-3} = 1{,}320$ is obtained in MeCN at 35.0 °C.[1i,9] It is well known that the P=O systems are generally more reactive than their P=S counterparts for several reasons, the so-called 'thio effect', which is mainly the electronegativity difference between O and S and favors O over S.[10]

The sequence of the second-order rate constants of the pyridinolyses of the eight P=S systems does not show systematic consistency with the NBO charge on the reaction

Table 1. Second-Order Rate Constants ($k_2 \times 10^4$/M^{-1} s^{-1}) of the Reactions of **3** [$Et_2P(=S)Cl$] with XC_5H_4N in MeCN at 55.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2 \times 10^4$	33.2±0.3	12.1±0.1	4.70±0.03	1.86±0.01	1.18±0.01	0.254±0.003	0.248±0.003	0.148±0.001	0.104±0.001	0.0950±0.0007

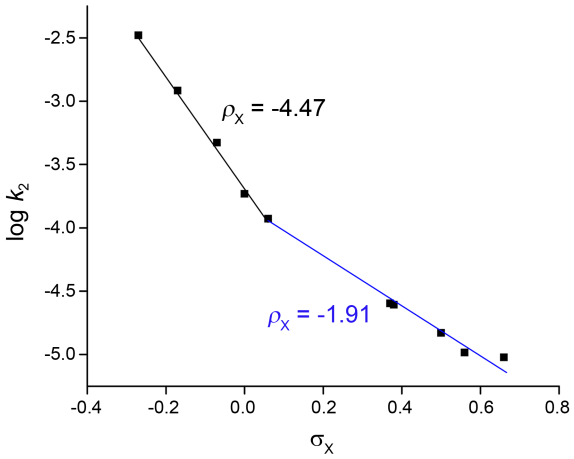


Figure 1. The Hammett plot (log k_2 *vs* σ_X) of the reactions of **3** [$Et_2P(=S)Cl$] with XC_5H_4N in MeCN at 55.0 ºC. The values of ρ_X are –4.47 ± 0.04 (r = 0.998) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph) and –1.91 ± 0.06 (r = 0.990) with X = (3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

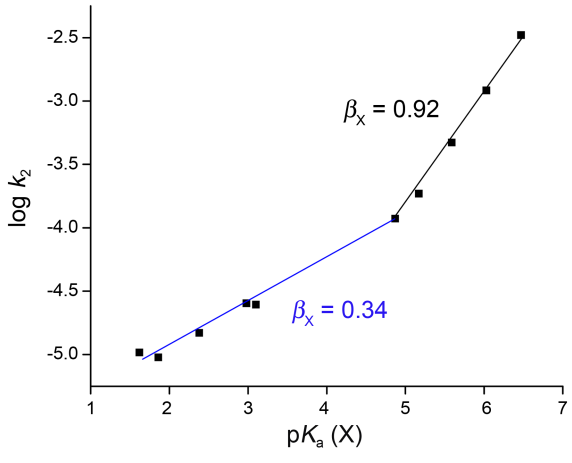


Figure 2. The Brönsted plot [log k_2 *vs* pK_a(X)] of the reactions of **3** [$Et_2P(=S)Cl$] with XC_5H_4N in MeCN at 55.0 ºC. The values of β_X are 0.92 ± 0.04 (r = 0.999) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph) and 0.34 ± 0.05 (r = 0.993) with X = (3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

center P atom or with the steric hindrance (size) of the two ligands. This means that the magnitude of the positive charge on the reaction center P atom and the size (or the steric effect) of the two ligands do not play any role to determine the reactivity of the pyridinolysis of $R_1R_2P(=S)Cl$-type substrates.[11] It is evident that the pyridinolysis of $R_1R_2P(=S)Cl$-type substrates is not charge controlled reaction. The dependence of the pyridinolysis rates upon the two ligands of the P=S systems is much smaller than those of their P=O counterparts: e.g., k_2(**1**)/k_2(**3**) = 7.8 with the P=S systems while $k_2[Me_2P(=O)Cl]/k_2[Et_2P(=O)Cl]$=800 with their P=O counterparts.[1h,i] These results indicate that the pyridinolysis rates of $R_1R_2P(=S)Cl$-type substrates in MeCN are not dependent upon one dominant factor but on many factors: ground state energy of the substrate, LUMO energy level of the substrate, electrophilicity of the substrate, steric effect of the two ligands, attacking orientation of the pyridine nucleophile, and/or geometry of the substrate, etc.

The substituent effects on the pyridinolysis mechanism of the P=S systems are surprising. The pyridinolyses of the P=S systems yield biphasic concave upward Hammett and Brönsted plots for substituent X variations in the nucleophiles for **1**, **2**, **3**, **4**, **6**, and **8**. In **5**, the Hammett and Brönsted plots for substituent X variations in the nucleophiles exhibited biphasic discrete two lines with a break region between X = H and 3-Cl, and the Hammett plots for substituent Y variations in the substrates exhibited biphasic concave downwards. In **8**, the Hammett plots for

Table 2. Summary of the Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) with C_5H_5N at 35.0 °C, NBO Charges at the Reaction Center P, and Selectivity Parameters (β_X and ρ_{XY}) for the Pyridinolyses of Eight $R_1R_2P(=S)Cl$-type in MeCN

Sub	R_1	R_2	$k_2 \times 10^{3a}$	charge at P	β_X	ρ_{XY}	ref.
1	Me	Me	0.744	1.180	0.97/0.27[b]	-	1h
2	MeO	MeO	1.54[c]	1.687	1.09/0.20[b]	-	1g
3	Et	Et	0.0960[d]	1.208	0.92/0.34[b]	-	this work
4	EtO	EtO	1.19[e]	1.701	1.02/0.29[b]	-	1g
5	Me	YC_6H_4O	14.3	1.432[f]	0.66-1.04/2.08-2.38[b]	–1.76/0/2.80/0[g]	1k
6	Ph	Ph	1.83	1.236	1.53/0.38[b]	-	1d
7	Ph	YC_6H_4O	11.2	1.462[f]	0.87-0.95	–0.46	1f
8	PhO	YC_6H_4O	0.333	1.661[f]	1.36-1.50/ 0.23-0.48[b]	2.42/5.14/–1.02/–0.04[g]	1j

[a]For the reaction with C_5H_5N, and with Y = H in the substrate (for **5**, **7**, and **8**) at 35.0 °C. [b]More/less basic pyridines. [c]Extrapolated value in the Arrhenius plot with kinetic data: k_2 = 2.23, 3.27, and 4.53×10^{-3} M^{-1} s^{-1} at 45.0, 55.0, and 65.0 °C, respectively. [d]Empirical value. See ref. 9. [e]Extrapolated value in the Arrhenius plot with kinetic data: k_2 = 1.70, 2.36, and 3.11×10^{-3} M^{-1} s^{-1} at 45.0, 55.0, and 65.0 °C, respectively. [f]The values with Y = H. [g]Stronger nucleophiles and weaker electrophiles/weaker nucleophiles and weaker electrophiles/stronger nucleophiles and stronger electrophiles/weaker nucleophiles and stronger electrophiles.

substituent Y variations in the substrates exhibited biphasic concave downwards. The substrate **7** only showed linear free energy correlations for both substituent X and Y variations. The substituent effects on the pyridinolysis mechanism of the P=S systems are more significant than the P=O systems:[12] e.g., their P=O counterparts of **2**, **3**, **4**, **6**, and **8** showed linear free energy correlations,[1a,d,g,i] while the P=O counterpart [$Me_2P(=O)Cl$] of **1** only showed concave upward free energy correlation.[1h]

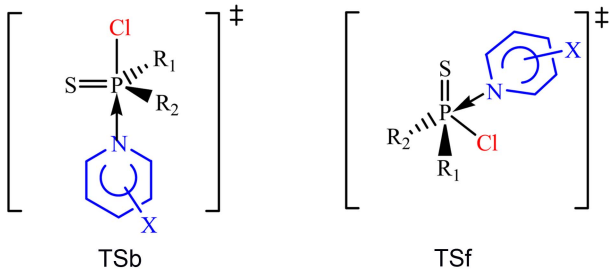
The CICs (ρ_{XY}) are defined as eqs. (2) where X and Y represent the substituents in the nucleophile and substrate, respectively.[8] The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and degree of tightness of the transition state (TS), respectively. In general, the ρ_{XY} has a negative value in a concerted S_N2 and a stepwise mechanism with a rate-limiting bond formation. However, it has a positive value for a stepwise mechanism with a rate-limiting leaving group departure from the intermediate. The magnitude of ρ_{XY} is inversely proportional to the distance between the nucleophile and substrate in the TS.[8]

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

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

The S_N2 reaction mechanism was proposed for the pyridinolysis of **7** on the basis of the negative sign of the CIC, ρ_{XY}. In **5** and **8**, the substituent effects on the reaction mechanism are divided into four blocks (*a*, *b*, *c*, and *d*) since the free energy correlations for both substituent X and Y variations showed break point or region: (*a*) stronger nucleophiles and weaker electrophiles; (*b*) weaker nucleophiles and weaker electrophiles; (*c*) stronger nucleophiles and stronger electrophiles; and (*d*) weaker nucleophiles and stronger electrophiles. In **5**, a stepwise mechanism with a rate-limiting bond formation for *a* block and with a rate-limiting bond breaking for *b*-*d* blocks was proposed. The null of ρ_{XY} value for *b* and *d* blocks was rationalized by the invariable distance between X and Y from the intermediate to the second TS. In **8**, the proposed mechanism was a stepwise process with a rate-limiting step change from bond breaking with *c* and *d* blocks to bond formation with *a* and *b* blocks.

In **1**, **2**, **4**, and **6**, the authors proposed a concerted mechanism with a dominant backside nucleophilic attack towards the Cl leaving group (TSb; Scheme 2) for more basic pyridines, and a concerted mechanism with a dominant frontside nucleophilic attack (TSf; Scheme 2) for less basic pyridines, in which the pyridine and Cl occupy adjacent spaces in the TS, on the basis of the concave upward Brönsted plots with smaller β_X values with less basic pyridines and greater values with more basic pyridines. In the present work, thus, the authors propose a concerted mechanism with a dominant backside nucleophilic attack (TSb) for more basic pyridines, and with a dominant frontside nucleophilic attack (TSf) for less basic pyridines on the basis of the same reason as for the pyridinolyses of **1**, **2**, **4**, and **6**.



Scheme 2. Backside attack TSb and frontside attack TSf.

The greater β_X value with more basic pyridines suggests a dominant frontside attack with greater bond formation compared to a dominant backside attack with less basic pyridines. It is well known that a weakly basic group has a greater apicophilicity so that an apical approach is favored for such nucleophiles.[1b,13] Since apical bonds are longer than equatorial bonds,[1b,13a] apical nucleophilic attack should lead to a looser P-N bond in the TBP-5C TS structure and hence a smaller magnitude of β_X is obtained, while the equatorial attack should lead to tighter P-N bond in the TBP-5C TS, resulting in a larger magnitude of β_X.[1b] It is the suggestion of the authors that the concave upward Hammett and Brönsted plots are diagnostic of a change in the attacking direction of the nucleophile depending on the substituents from backside to frontside.

In summary, the pyridinolysis of diethyl thiophosphinic chloride is investigated kinetically in acetonitrile at 55.0 °C. A concerted mechanism with a dominant backside nucleophilic attack (TSb) for more basic pyridines and with a dominant frontside nucleophilic attack (TSf) for less basic pyridines is proposed on the basis of concave upward free energy correlation and greater magnitudes of selectivity parameters with more basic pyridines. The pyridinolyses of eight $R_1R_2P(=S)Cl$-type substrates are reviewed to obtain systematic information on phosphoryl transfer reaction mechanism. The pyridinolysis rates of $R_1R_2P(=S)Cl$-type substrates are not dependent upon one dominant factor but on many factors.

Experimental Section

Materals. GR grade pyridines and HPLC grade acetonitrile (less than 0.005% water content) were used without further purification. Diethyl thiophosphinic chloride (**3**) was prepared as described previously.[2p,14]

Kinetic Procedure. Conductometric rate measurements were carried out using self-made computer-aided automatic A/D converter conductivity bridges. The pseudo-first-order rate constants (k_{obsd}) were determined using large excess of nucleophiles, [**3**] = 0.002 M and [XC_5H_4N] = 0.1-0.5 M. Each pseudo-first-order rate constants value (k_{obsd}) was averaged obtained from more than three runs, which were reproducible within ± 3%.

Product Analysis. Diethyl thiophosphinic chloride was reacted with excess 3-cyanopyridine, for more than 15 half-

lives at 55.0 °C in acetonitrile. Acetonitrile was removed under reduced pressure. The product was isolated by adding ether and insoluble fraction was collected. The product was purified to remove excess pyridine by washing several times with ether. Analytical and spectroscopic data of the product gave the following results:

$(C_2H_5)_2P(=S)N^+C_5H_4$-3-$CNCl^-$. Light-yellow gummy-substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.34 (6H, m, $2CH_3$), 1.95-2.31 (4H, m, $2CH_2$), 7.40 (s, 1H, pyridinium), 7.93 (s, 1H, pyridinium), 8.85, 8.75 (d, J = 4.0 Hz, 2H, pyridinium); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.74 (CH_3, ethyl), 32.77, 33.33 (CH_2, ethyl), 110.01 (CN), 116.31, 123.59, 139.19, 152.16, 152.72 (C=C, pyridinium); ^{31}P NMR (162 MHz, $CDCl_3$) δ 67.28 (1P, s, P=S); *m*/*z*, 258 (M^+).

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