Pyridinolysis of Dipropyl Chlorothiophosphate in Acetonitrile

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Continuing the kinetic studies of the pyridinolyses of dimethyl [**1**: $(MeO)_2P(=S)Cl$],[1] diethyl [**2**: $(EtO)_2P(=S)Cl$],[1] Y-aryl ethyl [**4**: $(EtO)(YC_6H_4O)P(=S)Cl$],[2] and Y-aryl phenyl [**5**: $(PhO)(YC_6H_4O)P(=S)Cl$][3] chlorothiophosphates, the nucleophilic substitution reactions of dipropyl chlorothiophosphate (**3**) with substituted X-pyridines are investigated kinetically in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1) to gain further systematic information into the reactivity and mechanism depending on the variation of the two ligands, R_1O and R_2O, where R_1 and R_2 are alkyl and/or phenyl (aryl). The numbering of the substrates of **1-5** follows the sequence of the size of the two ligands, R_1O and R_2O.

Results and Discussion

The reactions were carried out under pseudo-first-order conditions with a large excess of pyridine. The observed pseudo-first-order rate constants (k_{obsd}) for all reactions obeyed eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants were determined with at least five pyridine concentrations. The linear plots of eq. (1) suggest a lack of any base-catalysis or side reactions, and the overall reaction is described by Scheme 1.

$$k_{obsd} = k_0 + k_2 [XC_5H_4N] \tag{1}$$

The second-order rate constants [k_2 (M^{-1} s^{-1})] are summarized in Table 1. The Brönsted β_X value was calculated by

correlating $\log k_2$(MeCN) with $pK_a(H_2O)$,[4] which was justified theoretically and experimentally.[5] The substituent effects of the nucleophiles upon the pyridinolysis rates correlate with those for a typical nucleophilic substitution reaction where the stronger nucleophile leads to a faster rate. However, both the Hammett ($\log k_2$ *vs* σ_X; Fig. 1) and Brönsted [$\log k_2$ *vs* $pK_a(X)$; Fig. 2] plots are biphasic concave upwards with a break point at X = 3-Ph. The magnitudes of ρ_X ($= -5.27$) and β_X ($= 1.08$) values with the strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph) are much greater than those ($\rho_X = -1.80$ and $\beta_X = 0.31$) with the weakly basic pyridines (X = 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

The second-order rate constants (k_2) with unsubstituted pyridine (C_5H_5N) at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the substrate in the gas phase [B3LYP/6-311+G(d,p) level of theory],[6] summations
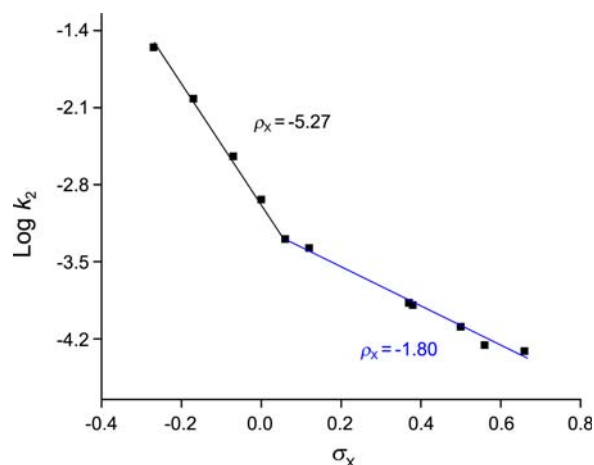

Figure 1. The Hammett plot ($\log k_2$ *vs* σ_X) of the reactions of dipropyl chlorothiophosphate (**3**) with X-pyridines in MeCN at 35.0 °C. The values of ρ_X are -5.27 ± 0.04 (r = 0.999) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph) and -1.80 ± 0.04 (r = 0.995) with X = (3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

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

Scheme 1. The reactions of dipropyl chlorothiophosphate (**3**) with substituted X-pyridines in MeCN at 35.0 °C.

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/M^{-1}$ s^{-1}) of the Reactions of Dipropyl Chlorothiophosphate (**3**) with XC_5H_4N in MeCN at 35.0 °C

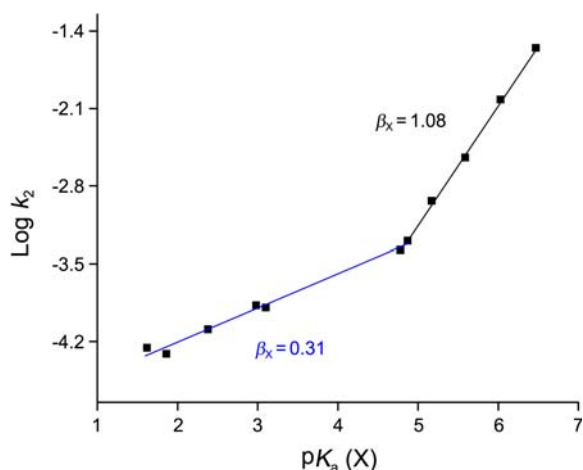| X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
k_2 $\times 10^4$	280 ± 1	95.6 ± 0.2	28.6 ± 0.1	11.6 ± 0.1	5.08 ± 0.02	4.22 ± 0.02	1.34 ± 0.01	1.28 ± 0.01	0.811 ± 0.004	0.555 ± 0.002	0.489 ± 0.002

Figure 2. The Brönsted plot [log k_2 *vs* pK_a(X)] of the reactions of dipropyl chlorothiophosphate (**3**) with X-pyridines in MeCN at 35.0 ºC. The values of β_X are 1.08 ± 0.03 (r = 0.999) with X = (4-MeO, 4-Me, 3-Me, H, 3-Ph) and 0.31 ± 0.05 (r = 0.994) with X = (3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

of the Taft's steric constants [$\Sigma E_S = E_S(R_1) + E_S(R_2)$] of the two ligands,[7] Brönsted coefficients (β_X), cross-interaction constants (CICs; ρ_{XY}),[8] and variation trends of the free energy relationships with X for the pyridinolyses of five $(R_1O)(R_2O)P(=S)Cl$-type chlorothiophosphates in MeCN are summarized in Table 2. When the magnitude of the positive charge of the reaction center P atom (i.e., electrophilicity) in the substrate plays an important role to determine the pyridinolysis rate, the sequence of the pyridinolysis rate should be **3** > **2** > **1** ≈ **4** > **5**. On the other hand, when the steric effects of the two ligands, R_1O and R_2O, play an important role, the sequence of the rate should be **1** > **2** > **3** > **4** > **5**. However, the observed sequence of the pyridinolyses rates of **1** > **2** ≥ **3** > **5** > **4** [the relative rate ratio of 11.2(**1**):8.7(**2**):8.5(**3**):2.4(**5**):1(**4**)] does not show systematic consistency with the NBO charge at P atom or ΣE_S of the two ligands. These results indicate that the pyridinolysis rates of $(R_1O)(R_2O)P(=S)Cl$-type substrates in MeCN are not dependent upon one dominant factor but on many factors. As observed in the pyridinolyses of chlorothiophosphates, the pyridinolysis rates of phosphinic chlorides

$[R_1R_2P(=O)Cl$-type],[9] chlorophosphates $[(R_1O)(R_2O)P(=O)Cl$-type],[1,10] thiophosphinic chlorides $[R_1R_2P(=S)Cl$-type],[9a,b,11] and phosphonochloridothioates $[R_1(R_2O)P(=S)Cl$-type][12] are not also dependent upon one predominant factor.

On the contrary, the anilinolysis rates of the chlorothiophsphates[13] are predominantly dependent upon the steric effects over the inductive effects of the two ligands. The greater the size of the two ligands, PhO,PhO(**5**) > EtO,PhO(**4**) > PrO,PrO(**3**) > EtO,EtO(**2**) > MeO,MeO(**1**), the anilinolysis rate becomes slower. The second-order rate constants for the reactions of five chlorothiophosphates with $C_6H_5NH_2$ in MeCN at 55.0 ºC gave the relative rate ratio of 9.9(**1**)[13a]:5.1(**2**)[13a]:3.0(**3**)[13b]:2.8(**4**)[13c]:1(**5**).[13d] The anilinolysis rates of phosphinic chlorides,[14] chlorophosphates,[13a,c,15] thiophosphinic chlorides,[16] phosphinates $[R_1R_2P(=O)(OPhZ)$-type],[17] and phosphonochloridothioates[18] are also qualitatively (or sometimes semi-quantitatively) dependent upon the steric effects of the two ligands.[19] The sensitivity to the steric effects of the two ligands on the anilinolysis rates of phosphinic (and thiophosphinic) chlorides is greater than that of chlorophosphates (and chlorothiophosphates), and that of P=O system is greater than that of P=S system. It seems that the intervening oxygen atom between the reaction center P atom and R_i in chlorophosphates reduces the sensitivity to the steric effects of the two ligands on the anilinolysis rates. In other words, the ligand, R_i, is directly bonded to P atom in (thio)phosphinic chloride, while the R_i group is bonded to the intervening oxygen atom which is bonded to P atom in chloro(thio)phosphate, and as a result, the available space for the attacking aniline in chloro(thio)-phosphate is greater than that in (thio)phosphinic chloride.

As seen in Table 2, the β_X values of **1**, **2**, and **3** are similar: β_X = 1.0-1.1 with the strongly basic pyridines and β_X = 0.2-0.3 with the weakly basic pyridines, strongly suggesting the same reaction mechanisms of the pyridinolyses of **1**, **2**, and **3**. The β_X (≈ 2.3) value of **4** with the strongly basic pyridines is the greatest one among all over the pyridinolyses of the P=O and P=S systems studied by this lab.[2] The β_X (= 1.4-1.5) values of **5** with the strongly basic pyridines are relatively great.[3] The β_X values of **4** and **5** with the weakly basic pyridines are somewhat greater than those of **1**, **2**, and **3**. The Hammett plots of **4** for the variation of substituent Y

Table 2. Summary of the Second-Order Rate Constants (k_2 with C_5H_5N at 35.0 ºC), NBO Charges at the Reaction Center P Atom, Summations of the Taft's Steric Constants (ΣE_S) of the Two Ligands, Brönsted Coefficients (β_X), CICs (ρ_{XY}), and Variation Trends of Free Energy Relationships with X for the Pyridinolyses of **1-5** in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-\Sigma E_S^d$	β_X	ρ_{XY}	Trend
1: $(MeO)_2P(=S)Cl$	1.54[b]	1.687	0	1.09/0.20[e]	–	V[g]
2: $(EtO)_2P(=S)Cl$	1.19[b]	1.701	0.14	1.02/0.29[e]	–	V
3: $(PrO)_2P(=S)Cl$	1.16	1.723	0.72	1.08/0.31[e]	–	V
4: $(EtO)(YC_6H_4O)P(=S)Cl$	0.137[c]	1.687[c]	2.55[c]	2.31-2.33/0.45-0.47[e]	0/0/0/0[f]	V
5: $(PhO)(YC_6H_4O)P(=S)Cl$	0.333[c]	1.661[c]	4.96[c]	1.36-1.50/0.23-0.48[e]	2.42/5.14/–1.02/–0.04[f]	V

[a]Second-order rate constant with unsubstituted pyridine (X = H) at 35.0 ºC. [b]Extrapolated value in the Arrhenius plot. [c]The value with Y = H. [d]Note that the value of ΣE_S is not '$E_S(R_1O) + E_S(R_2O)$' but '$E_S(R_1) + E_S(R_2)$' because of a lack of data of $E_S(R_iO)$. [e]Strongly basic/weakly basic pyridines. [f]Stronger nucleophiles and weaker electrophiles/weaker nucleophiles and weaker electrophiles/stronger nucleophiles and stronger electrophiles/weaker nucleophiles and stronger electrophiles. [g]The symbol of V indicates biphasic concave upward free energy correlation with a break point for the variation of X in the nucleophiles.

in the substrate are biphasic concave upwards with a break (minimum) point at Y = H while those of **5** are concave downwards with a break point at Y = H. Thus, the four values of CICs, ρ_{XY}, were obtained for both **4** and **5**. In **4**, the CICs, ρ_{XY} are all null in spite of the biphasic free energy correlations for both substituent X and Y variations, since the ρ_X values with both the strongly and weakly basic pyridines are almost constant. This reaction is the only one, having all $\rho_{XY} = 0$ with four blocks until now: stronger nucleophiles and weaker electrophiles, weaker nucleophiles and weaker electrophiles, stronger nucleophiles and stronger electrophiles, and weaker nucleophiles and stronger electrophiles. Herein, the null of ρ_{XY} value implies that the distance between X and Y does not vary from the intermediate to the second transition state (TS), in which the reaction proceeds through a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate. A frontside attack TSf (Scheme 2) was proposed with the strongly basic pyridines based on the considerably great magnitudes of β_X value and a backside attack involving in-line-type TSb (Scheme 2) was proposed with the weakly basic pyridines based on the relatively small magnitudes of β_X. In **5**, a stepwise process was proposed involving a rate-limiting step change from bond breaking with the weaker electrophiles based on the large positive ρ_{XY} value to bond formation with the stronger eletrophiles based on the negative ρ_{XY} value. The nonlinear free energy correlations of biphasic concave upward plots with X in the nucleophiles were rationalized by a change in the attacking direction of the nucleophile from a backside with less basic pyridines to a frontside attack with more basic pyridines.

In the present work, the free energy correlations for substituent X variations in the pyridines are biphasic concave upwards. The biphasic concave upward free energy relationships are interpreted as a change of the nucleophilic attacking direction from a frontside attack TSf with the strongly basic pyridines based on the considerably great magnitudes of β_X value to a backside attack involving in-line-type TSb with the weakly basic pyridines based on the relatively small magnitudes of β_X in a concerted process, the same mechanism as in **1** and **2**.

In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism, such as parallel reactions where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of the biphasic concave downward plot is diagnostic of a rate-limiting step change from
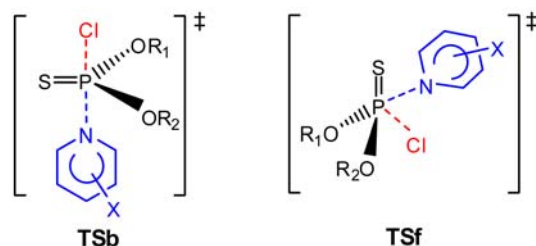
bond breaking with less basic nucleophiles to bond formation with more basic nucleophiles.[20] It is the suggestion of the authors that the concave upward Hammett and Brönsted plots can also be diagnostic of a change in the attacking direction of the nucleophile depending on the substituents from backside to frontside. It is worthy of note that a frontside attack TSf yields greater magnitudes of ρ_X and β_X values compared to a backside attack.[21]

In summary, the kinetic studies on the pyridinolysis of dipropyl chlorothiophosphate have been carried out in MeCN at 35.0 °C. The free energy correlations are biphasic concave upwards with a break point at X = 3-Ph. A concerted S_N2 mechanism is proposed with a change of the attacking direction of the X-pyridine from a frontside attack with the strongly basic pyridines to a backside attack with the weakly basic pyridines.

Experimental Section

Materials. Dipropyl chlorothiophosphate, GR grade pyridines and HPLC grade acetonitrile (water content is less than 0.005%) were used for kinetic studies without further purification.

Kinetic Procedure. Rates were measured conductometrically at 35.0 °C. The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. The pseudo-first-order rate constants, k_{obsd}, were measured by curve fitting analysis in origin program with a large excess of pyridines, [substrate] = 1×10^{-3} M and $[XC_5H_4N] = (0.1\text{-}0.3)$ M. Second-order rate constants, k_2, were obtained from the slope of a plot of k_{obsd} *vs* [X-pyridine] at least with five concentrations of pyridine. The pseudo-first-order rate constant values (k_{obsd}) were the average of three runs that were reproducible within ± 3%.

Product Analysis. Dipropyl chlorothiophosphate was reacted with excess pyridine, for more than 15 half-lives at 35.0 °C in MeCN. 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:

$[(PrO)_2P(=S)NC_5H_5]^+Cl^-$. Colorless liquid; ^1H NMR (400 MHz, CDCl$_3$) δ 0.84-0.97 (6H, m, 2CH$_3$, Pr), 1.60-1.71 (4H, m, 2CH$_2$, Pr), 4.03-4.12 (4H, m, 2CH$_2$, Pr), 8.02 (2H, t, $J = 7.6$ Hz, pyridinium), 8.50 (1H, t, $J = 8.0$ Hz, pyridinium), 8.87 (2H, d, $J = 9.6$ Hz, pyridinium); ^{13}C NMR (100 MHz, CDCl$_3$) δ 9.88 (CH$_3$, Pr), 23.13 (CH$_2$, Pr), 70.75 (CH$_2$, Pr), 127.22, 128.42, 141.05, 145.81 (C=C, pyridinium); ^{31}P NMR (162 MHz, CDCl$_3$) δ 58.30 (s, 1P, P=S); *m/z* 295 (M$^+$).

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Scheme 2. Backside attack TSb and frontside attack TSf.

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