Kinetics and Mechanism of the Pyridinolysis of Diethyl Isothiocyanophosphate in Acetonitrile[†]

Keshab Kumar Adhikary and Hai Whang Lee[*]

*Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr*
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The kinetics and mechanism of the pyridinolysis (XC_5H_4N) of diethyl isothiocyanophosphate are investigated in acetonitrile at 55.0 ℃. The Hammett and Brönsted plots for substituent X variations in the nucleophiles exhibit the two discrete slopes with a break region between X = 3-Ac and 4-Ac. These are interpreted to indicate a mechanistic change at the break region from a concerted to a stepwise mechanism with rate-limiting expulsion of the isothiocyanate leaving group from a trigonal bipyramidal pentacoordinated intermediate. The relatively large β_X values with more basic and less basic pyridines imply much greater fraction of frontside nucleophilic attack TSf than that of backside attack TSb.

Key Words : Phosphoryl transfer reaction, Pyridinolysis, Diethyl isothiocyanophosphate, Discrete biphasic free energy relationship

Introduction

In a previous work, the kinetics and mechanism of the pyridinolysis of Y-aryl phenyl isothiocyanophosphates [**2**; $(YC_6H_4O)(PhO)P(=O)NCS$] involving a leaving group of isothiocyanate (NCS^-) in acetonitrile (MeCN) at 55.0 ℃ were reported by this lab.[1] Surprising substituent effects of the nucleophiles and substrates were found. The Hammett and Brönsted plots for substituent X variations in the nucleophiles exhibited biphasic concave upwards with a break point ($\sigma_X = 0.2$). On the contrary, the Hammett plots for substituent Y variations in the substrates exhibited biphasic concave downwards with a break point at Y = H. For electron-donating Y substituents ($\sigma_Y < 0$) the Hammett coefficients are positive ($\rho_Y > 0$) and cross-interaction constants (CICs)[2] are negative ($\rho_{XY} < 0$), while those for electron-withdrawing Y substituents ($\sigma_Y > 0$) are negative ρ_Y with positive ρ_{XY}. These are interpreted to indicate mechanistic change at the breakpoint from a concerted to a stepwise mechanism with a rate-limiting expulsion of the NCS^- group from a trigonal bipyramidal pentacoordinated (TBP-5C) intermediate. In the present work, the nucleophilic substitution reactions of diethyl isothiocyanophosphate (**1**) with X-pyridines are kinetically investigated in MeCN at 55 ℃ (Scheme 1). The interest is centered into the mechanistic change and/or transition (TS) structure variation associated with the substituent X changes in the nucleophiles for the phosphoryl transfer reactions involving a leaving group of isothiocyanate by determining the Hammett (ρ_X) and Brönsted (β_X) coefficients. The kinetic results of the pyridinolyses of **1** and **2** are compared with those of diethyl [**1'**; $(EtO)_2P(=O)Cl$][3] and Y-aryl phenyl [**2'**; $(YC_6H_4O)(PhO)P(=O)Cl$][4] chlorophosphates involving a

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

Scheme 1. The pyridinolysis of diethyl isothiocyanophosphate (**1**) in MeCN at 55.0 ℃.
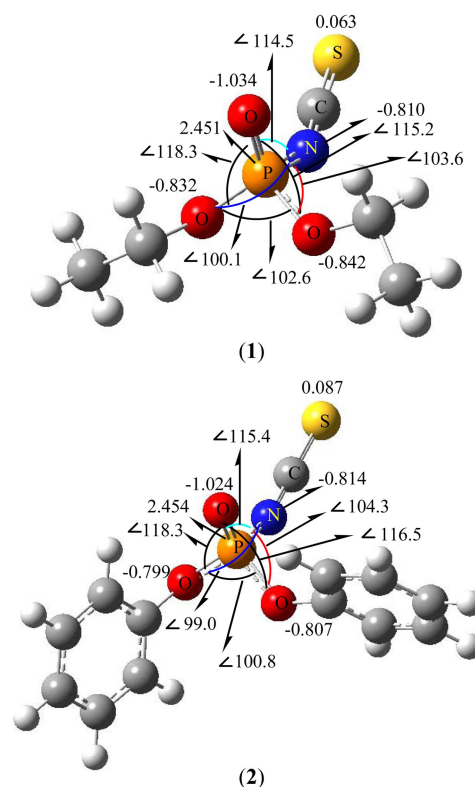
Figure 1. The B3LYP/6-311+G(d,p) geometries of diethyl (**1**) and diphenyl (**2**) isothiocyanophosphate in the gas phase.

Table 1. The Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) of the Reactions of Diethyl Isothiocyanophosphate (**1**) with XC$_5$H$_4$N in MeCN at 55.0 ºC

X	4-MeO	4-Me	H	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2 \times 10^3$	292 ± 1	97.9 ± 0.4	8.87 ± 0.01	9.05 ± 0.01	0.103 ± 0.001	0.0900 ± 0.0003	0.320 ± 0.003	0.0943 ± 0.0003	0.0365 ± 0.0002

leaving group of chloride (Cl$^-$) with regard to the leaving group mobility, selectivity parameter, and mechanism.

The B3LYP/6-311+G(d,p) geometries, bond angles, and natural bond order (NBO) charges of **1** and **2** in the gas phase[5] are shown in Figure 1. The MO theoretical structures show that the three oxygens and nitrogen have more or less distorted tetrahedral geometry with the phosphorus atom at the center. The degree of distortion of **2** ($\Delta\delta = 0.42$) is greater than that of **1** ($\Delta\delta = 0.38$) due to larger size of the two phenoxy ligands compared to the two ethoxy ligands.[6]

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 the reactions obeyed Eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants (k_2) were determined with at least five pyridine concentrations. The linear plots of Eq. (1) suggest a lack of any base-catalysis or side reaction, and the overall reaction is described by Scheme 1.

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

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$_2$O).[7] This procedure of using pK_a(H$_2$O) instead of pK_a(MeCN) values of X-pyridines has been shown to be justified theoretically and experimentally since there is a practically constant difference between the two sets of pK_a's in H$_2$O and in MeCN for various X-pyridines so that the slopes in the two solvents differ insignificantly.[8] The pyridinolysis rates are not consistent with a typical nucleophilic substitution reaction. The rate becomes slower with a weaker nucleophile for X = (4-MeO, 4-Me, H, 3-MeO, 3-Cl, 3-Ac). However, the rate with X = 4-Ac is unusually 3.6 times faster than with X = 3-Ac in spite of greater basicity of 3-acetylpyridine compared to 4-actylpyridine. After a break region, the rate becomes slower with a weaker nucleophile for X = (4-Ac, 3-CN, 4-CN). Thus, both the Hammett (Fig. 2; log k_2 *vs* σ_X) and Brönsted [Fig. 3; log k_2 *vs* pK_a(X)] plots for substituent X variations in the nucleophiles exhibit the two discrete slopes with a break region between X = 3-Ac and 4-Ac, giving $\rho_X = -5.35 \pm 0.28$ (r = 0.986) and -5.71 ± 0.14 (r = 0.977), and $\beta_X = 0.97 \pm 0.24$ (r = 0.990) and 0.63 ± 0.53 (r = 0.616) with X = (4-MeO, 4-Me, H, 3-MeO, 3-Cl, 3-Ac) and X = (4-Ac, 3-CN, 4-CN), respectively. The selectivity parameters with more basic pyridines are slightly smaller than those with less basic pyridines. These kinetic results strongly suggest a change of the reaction mechanism from more basic to less basic
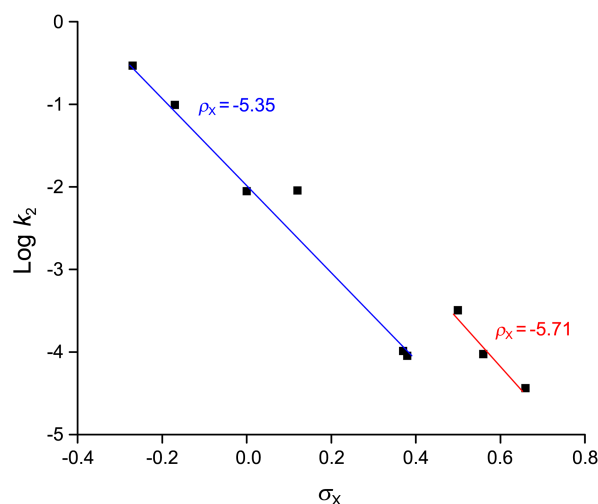
Figure 2. The Hammett plot (log k_2 *vs* σ_X) of the reactions of diethyl isothiocyanophosphate (**1**) with X-pyridines in MeCN at 55.0 ºC.
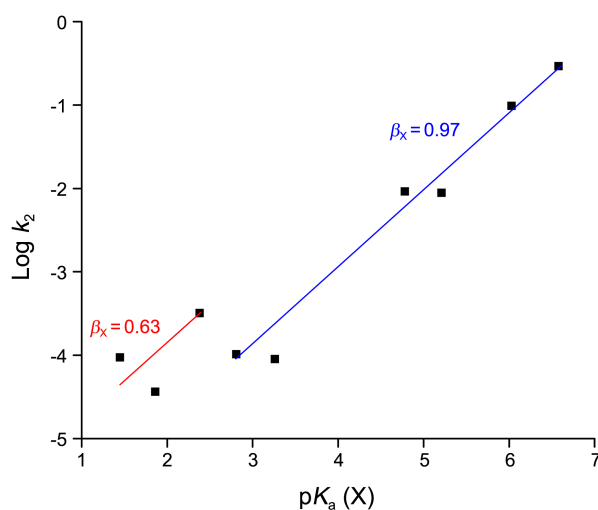
Figure 3. The Brönsted plot [log k_2 *vs* pK_a(X)] of the reactions of diethyl isothiocyanophosphate (**1**) with X-pyridines in MeCN at 55.0 ºC.

pyridines.

The second-order rate constants (k_2) with unsubstituted pyridine (C$_5$H$_5$N) at 55.0 ºC, NBO charges at the reaction center P atom in the gas phase [B3LYP/6-311+G(d,p) level of theory],[5] summations of Taft's steric constants of the two ligands [$\Sigma E_S = E_S(R_1) + E_S(R_2)$ from E_S(Et) = −0.07 and E_S(Ph) = −2.48],[9] Brönsted coefficients (β_X), and CICs (ρ_{XY})[2] for the pyridinolyses (XC$_5$H$_4$N) of **1**, **1'**, **2**, and **2'** in MeCN are summarized in Table 2. The pyridinolysis rate ratios of k(**1'**)/k(**1**) = 12 and k(**2'**)/k(**2**) = 257 indicate that the leaving group mobility of chloride is greater than that

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

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-\Sigma E_S{}^e$	β_X	ρ_{XY}
1: $(EtO)_2P(=O)NCS$	8.87	2.451	0.14	0.97/0.63[f]	–
1': $(EtO)_2P(=O)Cl$	107[b]	2.236	0.14	0.73	–
2: $(YC_6H_4O)(PhO)P(=O)NCS$	3.02[c]	2.454[c]	4.96[c]	1.13-1.28/0.08-0.22[g]	−1.42/−1.81/3.16/1.40[h]
2': $(YC_6H_4O)(PhO)P(=O)Cl$	775[c,d]	2.230[c]	4.96[c]	0.16-0.18	−0.15

[a]The second-order rate constant with unsubstituted pyridine in MeCN at 55.0 °C. [b]Extrapolated value in the Arrhenius plot with kinetic data: $k_2 = 37.9$, 52.8, and 78.2×10^{-3} $M^{-1} s^{-1}$ at 25.0, 35.0, and 45.0 °C, respectively. See ref. 3. [c]The value with Y = H. [d]Extrapolated value in the Arrhenius plot with kinetic data: $k_2 = 37.1$, 94.0, and 135×10^{-3} $M^{-1} s^{-1}$ at 5.0, 15.0, and 25.0 °C, respectively. See ref. 4. [e]Note that the value of ΣE_S is not $E_S(R_1O) + E_S(R_2O)$ but $E_S(R_1) + E_S(R_2)$ since the data of Taft's steric constants of R_iO are not available. [f]X = (4-MeO, 4-Me, H, 3-MeO, 3-Cl, 3-Ac)/(4-Ac, 3-CN, 4-CN). [g]X = (4-MeO, 4-Me, 3-Me, H, 3-Ph)/(3-Ac, 3-Cl, 4-Ac, 4-CN). [h]Stronger nucleophiles and weaker electrophiles/weaker nucleophiles and weaker electrophiles/stronger nucleophiles and stronger electrophiles/weaker nucleophiles and stronger electrophiles.

of isothiocyanate. In other words, chloride is a better leaving group compared to isothiocyanate. The leaving group mobility is strongly dependent upon the nature of the two ligands. The magnitude of the NBO charge of the reaction center P atom does not play any role to determine the leaving group mobility. The rate ratio of $k(\mathbf{1})/k(\mathbf{2}) = 2.9$ is opposite to that of $k(\mathbf{1'})/k(\mathbf{2'}) = 0.14$, implying that the major factor to decide the reactivity is different between the two systems. The rate ratio of $k(\mathbf{1})/k(\mathbf{2}) = 2.9$ seems to indicate that the steric effects of the two ligands are the predominant factor to decide the reactivity, i.e., the greater the two ligands, the rate becomes slower.[10] The rate ratio of $k(\mathbf{1'})/k(\mathbf{2'}) = 0.14$ is atypical result.[11]

The pyridinolyses of **1'** and **2'** involving the chloride leaving group yielded linear free energy relationships for substituent X (and Y) variations in the nucleophiles (and substrates). A concerted mechanism with both frontside and backside nucleophilic attack was proposed for the reactions of **1'** on the basis of the magnitudes of relatively large β_X (= 0.73) value.[3] A concerted mechanism with an early TS involving backside nucleophilic attack towards the Cl leaving group was proposed on the basis of small negative CIC ($\rho_{XY} = -0.15$)[12] and small values of Brönsted coefficients ($\beta_X = 0.16$-0.18) for the pyridinolysis of **2'**.[4]

Chloride should be a far better leaving group than isothiocyanate. The change of the leaving group from chloride to that of a lower leaving ability, isothiocyanate, can cause a change in mechanism from a concerted to a stepwise process with a rate-limiting breakdown of the TBP-5C intermediate. This is in accord with the well established trend of the mechanistic change depending on the leaving group ability: the lower the leaving ability of the leaving group, the greater is the tendency for a stepwise mechanism with a rate-limiting expulsion of the leaving group from the intermediate.[13] The Hammett plots of the pyridinolyses of **2** involving isothiocyanate leaving group are biphasic concave downwards with Y: (i) for electron-donating substituent Y, the large negative ρ_{XY} (= −1.42 and −1.81) values coupled with positive ρ_Y (= 1.65-2.49) values suggest a concerted process, an associative S_N2 process with a greater degree of bond-making than bond-cleavage in the TS; (ii) for electron-withdrawing substituent Y, the large positive ρ_{XY} (= +3.16
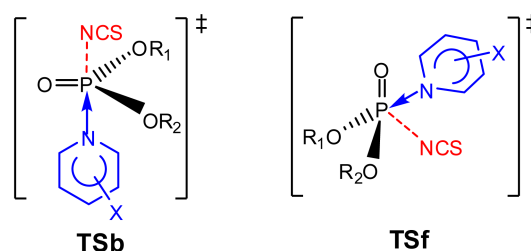
Scheme 2. Backside attack TSb and frontside attack TSf.

and +1.40) values coupled with negative ρ_Y (= −2.29 to −3.81) values suggest a stepwise mechanism with a rate-limiting leaving group departure from the intermediate.[1] The Hammett and Brönsted plots are biphasic concave upwards with X: (i) for more basic pyridines, frontside nucleophilic attack TSf (Scheme 2) was proposed on the bases of large β_X (= 1.13-1.28) values; (ii) for less basic pyridines, backside attack TSb (Scheme 2) was proposed on the bases of small β_X (= 0.08-0.22) values, suggesting an equatorial nucleophilic attack for more basic pyridines in contrast to an apical attack for less basic pyridines.[1] It is well known that a weakly basic group has a greater apicophilicity so that apical approach is favored for such nucleophiles.[14] Since the apical bonds are longer than the equatorial bonds,[14] the apical nucleophilic attack should lead to a looser P–N bond in the TBP-5C structure and hence a smaller magnitude of β_X.

In the present work of **1**, the Hammett and Brönsted plots for substituent X variations in the nucleophiles show the two *discrete* slopes with relatively large β_X values: $\beta_X = 0.97$ and 0.63 with more basic (X = 4-MeO, 4-Me, H, 3-MeO, 3-Cl, 3-Ac) and less basic pyridines (X = 4-Ac, 3-CN, 4-CN), respectively.[15] Note that the two β_X values are comparable regardless of the nature of the substituent X, more basic or less basic pyridines.[15] As observed in the present work, the discrete two slopes for substituent X variations in the nucleophiles with relatively large β_X (= 0.66-1.04 and 2.13-2.14 with more basic and less basic pyridines, respectively) values were observed for the reactions of Y-O-aryl methyl phosphonochloridothioates $[Me(YC_6H_4O)P(=S)Cl]$ with X-pyridines in MeCN.[16] The obtained CICs (ρ_{XY}) are −1.76, ~0, 2.80, and ~0 with stronger nucleophiles and weaker electrophiles, weaker nucleophiles and weaker electrophiles,

stronger nucleophiles and stronger electrophiles, and weaker nucleophiles and stronger electrophiles, respectively.[17] The β_X values are 0.7-1.0 and 1.0-1.1 with more basic and less basic pyridines, respectively.[17] A concerted mechanism (or a stepwise mechanism with a rate-limiting bond formation) was proposed for stronger nucleophiles and weaker electrophiles,[18] while a stepwise mechanism with a rate-limiting bond breaking was proposed for weaker nucleophiles and weaker electrophiles, stronger nucleophiles and stronger electrophiles, and weaker nucleophiles and stronger electrophiles on the basis of the sign and magnitudes of CICs (ρ_{XY}).[16]

In the present work, thus, the authors propose a concerted S_N2 mechanism for more basic pyridines and a stepwise mechanism with a rate-limiting leaving group departure from the TBP-5C intermediate for less basic pyridines on the basis of the pyridinolysis mechanism of Y-*O*-aryl methyl phosphonochloridothioates, showing same free energy relationship as the present work with X. The relatively large β_X values with more basic and less basic pyridines imply much greater fraction of frontside nucleophilic attack TSf than that of backside attack TSb (Scheme 2).

The activation parameters determined with rate constants at three temperatures are summarized in Table 3. The values of enthalpy of activation and entropy are comparable to the corresponding values for the reaction with better leaving group (Cl⁻), e.g. $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values are 6.3 kcal mol⁻¹ and -44 eu for **1'** with X = H.[3] The relatively small value of enthalpy of activation and large negative value of activation of entropy are general in the phosphoryl transfer reaction.

Experimental Section

Materials. HPLC grade MeCN (less than 0.005% water content) was used without further purification. The X-pyridines (GR grade) were used without further purifications. The substrate was synthesized as previously mentioned way,[1,19] where ethyl dichlorophosphate (1.73 g; 0.01 mole)

Table 3. Activation Parameters[a] for the Pyridinolysis of Diethyl Isothiocyanophosphate (**1**) with XC₅H₄N in MeCN

X	t/°C	$k_2 \times 10^3$/M⁻¹ s⁻¹	$\Delta H^{\neq}$/ kcal mol⁻¹	$-\Delta S^{\neq}$/ cal mol⁻¹ K⁻¹
	35.0	147 ± 1		
4-MeO	45.0	217 ± 1	6.3 ± 0.4[b]	42 ± 1[b]
	55.0	292 ± 1		
	35.0	56.0 ± 0.2		
4-Me	45.0	76.7 ± 0.5	5.0 ± 0.3	48 ± 1
	55.0	97.9 ± 0.4		
	35.0	5.11 ± 0.01		
H	45.0	6.90 ± 0.03	4.9 ± 0.2	53 ± 1
	55.0	8.87 ± 0.01		
	35.0	0.0792 ± 0.003		
4-Ac	45.0	0.167 ± 0.002	13.4 ± 0.3	34 ± 1
	55.0	0.320 ± 0.003		

[a]Calculated by the Eyring equation. [b]Standard deviation

was taken into a round-bottomed flask with MeCN (25 mL) as solvent. Equivalent amount of potassium thiocyanate solution were taken into another flask with 25 mL MeCN. Then the potassium thiocyanate solution was added to ethyl dichlorophosphate solution dropwise with a vigorous stirring in a cooling bath at 0 °C. The reaction was allowed for 3 hr after completion of addition of potassium thiocyanate. Solvent was evaporated under reduced pressure and 30 mL ethyl ether was added to it. Insoluble potassium chloride was removed by filtration. The product was isolated by column chromatography using 50% ethylacetate and *n*-hexane after evaporation of ether under reduced pressure. Product was finally isolated by removing solvent under vacuum using oil diffusion pump. The analytical data of the substrate are given bellow (see supplementary materials):

(C₂H₅O)₂P(=O)NCS. Reddish brown colored oily liquid; ¹H NMR (400 MHz, CDCl₃) δ 1.39 (CH₃, m, 6H), 4.22 (CH₂, m, 4H); ¹³C NMR (50 MHz, CDCl₃) δ 15.94 (CH₃, aliphatic, 2C, d, J = 6.85 Hz), 65.16 (CH₂, aliphatic, 2C, d, J = 6.45 Hz), 175.95 (NCS, 1C, s); ³¹P NMR (162 MHz, CDCl₃) δ −12.90 (1P, s); v_{max} (thin film), 2987 cm⁻¹ (C-H, str. aliphatic), 1998 cm⁻¹ (NCS, broad str. region), 1292 cm⁻¹ (P=O str.), 1018 cm⁻¹ (P-O-aliphatic str.); *m/z* 195 (M⁺).

Kinetic Procedure. Rates were measured conductometrically at 55.0 °C using a computer controlled conductivity bridge constructed in this lab. Pseudo-first-order rate constants, k_{obsd}, were measured by using curve-fitting method in ORIGIN program. Pseudo-first-order rate constants were determined with large excess of pyridines in acetonitrile; [substrate] = 1 × 10⁻³ M and [X-pyridine] = (0.10-0.25) M. Pseudo-first-order rate constants were reproducible within ± 3%.

Product Analysis. Diethyl isothiocyanophosphate (0.005 M) was reacted with pyridine (0.005 M) in MeCN at 55.0 °C. After more than 15 half-lives, product was isolated by washing with solvent using ethylacetate and *n*-hexane mixture (50%) with several attempts. Finally, the product was isolated by washing with *n*-hexane. The analytical data of the product gave the following results (see supplementary materials):

[(C₂H₅O)₂P(=O)N⁺C₅H₅]⁻NCS. Reddish-brown gummy liquid; ¹H NMR (400 MHz, CD₃CN): δ 1.29 (6H, m, CH₃), 4.05 (4H, m, CH₂), 7.98-8.74 (5H, m, pyridine); ¹³C NMR (100 MHz, CD₃CN) δ 16.54 (2C, s, CH₃), 64.25 (2C, s, CH₂), 128.43-147.65 (C=C, pyridine), 192.26 (1C, s, NCS); ³¹P NMR (162 MHz, CD₃CN) δ 10.34 (1P, s, P=O); v_{max} (thin film), 3070-3140 cm⁻¹ (C-H, str. aromatic), 2870-2984 cm⁻¹ (C-H, str. aliphatic), 2062 cm⁻¹ (NCS, broad str. region), 1226 cm⁻¹ (P=O str.); 1165, 1026, 969 cm⁻¹ (P-O-aliphatic str.); LC-MS, *m/z* 274 (M⁺).

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11. The faster pyridinolysis rate of **2'** than that of **1'** is unusual; $k(\mathbf{2'})/k(\mathbf{1'}) = 7.2$ in MeCN at 55.0 °C. On the contrary, the anilinolysis rate of **1'** is faster than that **2'**; $k(\mathbf{1'})/k(\mathbf{2'}) = (2.82 \times 10^{-3})/(8.91 \times 10^{-4}) = 3.2$ in MeCN at 55.0 °C: (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1999**, 765. (b) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2008**, *21*, 544.
12. The magnitude of ρ_{XY} value is inversely proportional to the distance between X and Y through the reaction center, and the negative sign of ρ_{XY} implies that the reaction proceeds through a concerted mechanism or a stepwise mechanism with a rate-limiting bond formation, while a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate with the positive sign of ρ_{XY}. The value of $\rho_{XY} = -0.7$ is a typical one for S$_N$2 process.
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15. The magnitude of ρ_X (= -5.35) with more basic pyridines is smaller than that ($\rho_X = -5.71$) with less basic pyridines. On the contrary, the magnitude of β_X (= 0.97) with more basic pyridines is greater than that ($\beta_X = 0.63$) with less basic pyridines. In general, the magnitude of ρ_X is proportional to that of β_X, since the value of σ_X is almost inversely proportional to that of pK_a(X). In the present work, however, there is no linear correlation between σ_X and pK_a(X) values foe studied less basic pyridines: σ_X(X) = 0.50(4-Ac); 0.56(3-CN); 0.66(4-CN) while pK_a(X) = 2.38(4-Ac); 1.45(3-CN); 1.86(4-CN). The correlation coefficient (r = 0.616) of β_X with less basic pyridines is much less than unity, and the calculated value of β_X with less basic pyridines is unusually smaller than that with more basic pyridines. The authors suggest that the real β_X value with less basic pyridines would be slightly larger than that with more basic pyridines.
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17. The CIC of $\rho_{XY} = \partial\rho_X/\partial\sigma_Y = 0$ can be occurred when: (i) X and Y are apart too far to interact, resulting in the absence of the cross-interaction between X and Y; (ii) the distance between X and Y does not vary, resulting in the invariable of the cross-interaction between X and Y. Herein, the null of ρ_{XY} value indicates a *special* stepwise mechanism with a rate-limiting leaving group departure from the intermediate where the distance between X and Y does not vary from the intermediate to the second TS.
18. A concerted, S$_N$2, process is more plausible than a stepwise mechanism with a rate-limiting bond formation since the ρ_{XY} observed exhibited a rather large negative value. For more details, see refs. 2.
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