

Kinetics and Mechanism of Pyridinolysis of *O,O*-Diethyl *S*-Aryl Phosphorothioates

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The kinetic studies on the reactions of *O,O*-diethyl *Z*-*S*-aryl phosphorothioates with X-pyridines have been carried out in dimethyl sulfoxide. The free energy correlations with X in the nucleophiles are biphasic concave upwards with a break point at X = H, while those for substituent Z variations in the leaving groups are linear. The negative sign of ρ_{XZ} implies that the reaction proceeds through a concerted mechanism for both the strongly and weakly basic pyridines. The biphasic concave upward free energy relationships with X are rationalized by a change in the nucleophilic attacking direction from frontside with the strongly basic pyridines to backside with the weakly basic pyridines.

Key Words : Biphasic concave upward free energy correlation, Phosphoryl transfer reaction, Pyridinolysis, *O,O*-Diethyl *S*-aryl phosphorothioates, Cross-interaction constant

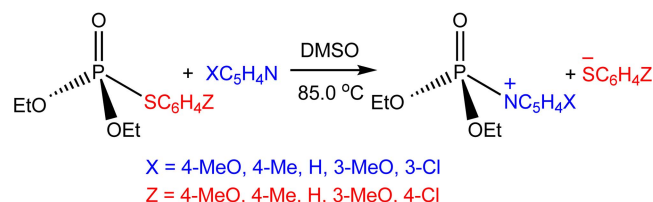
Introduction

The authors reported that the substituent effects of the nucleophiles (X) and/or substrates (Y) and/or leaving groups (Z) upon the kinetics and mechanism of the pyridinolyses in the phosphoryl and thiophosphoryl transfer are exceptionally significant. In the present work, the nucleophilic substitution reactions of *O,O*-diethyl *Z*-*S*-aryl phosphorothioates (**2**) with X-pyridines are investigated kinetically in dimethyl

sulfoxide (DMSO) at 85.0 ± 0.1 °C (Scheme 1) to obtain further systematic information on the phosphoryl transfer reactions and substituent effects of the nucleophiles and leaving groups on the reaction mechanism, as well as to compare the relevant pyridinolyses of *O,O*-dimethyl [**1**: $(\text{CH}_3\text{O})_2\text{P}(=\text{O})\text{SC}_6\text{H}_4\text{Z}$]^{1a} and *O,O*-diphenyl [**3**: $(\text{C}_6\text{H}_5\text{O})_2\text{P}(=\text{O})\text{SC}_6\text{H}_4\text{Z}$]^{1b} *Z*-*S*-aryl phosphorothioates in DMSO and MeCN, respectively.

Results and Discussion

Tables 1-3 list the second-order rate constants ($k_2/\text{M}^{-1} \text{s}^{-1}$), Hammett (ρ_X) and Brönsted (β_X) coefficients with X, and Hammett coefficients (ρ_Z) with Z, respectively. The substituent X and Z effects on the rates are in accord with those for a typical nucleophilic substitution reaction with partial positive charge development at the nucleophilic N atom and with partial negative charge development at the leaving group S atom in the transition state (TS). The Brönsted (Fig.



Scheme 1. Pyridinolysis of *O,O*-diethyl *Z*-*S*-aryl phosphorothioates (**2**) in DMSO at 85.0 °C.

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/\text{M}^{-1} \text{s}^{-1}$) of the Reactions of **2** with X-Pyridines in DMSO at 85.0 °C

X \ Z	4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	0.936 ± 0.001	1.47 ± 0.01	2.05 ± 0.01	2.77 ± 0.02	4.26 ± 0.01
4-Me	0.695 ± 0.001	1.06 ± 0.01	1.38 ± 0.02	1.91 ± 0.01	2.93 ± 0.03
H	0.387 ± 0.002	0.571 ± 0.001	0.774 ± 0.001	1.01 ± 0.01	1.51 ± 0.01
3-MeO	0.329 ± 0.001	0.462 ± 0.002	0.641 ± 0.001	0.798 ± 0.001	1.17 ± 0.01
3-Cl	0.233 ± 0.001	0.311 ± 0.001	0.404 ± 0.002	0.511 ± 0.001	0.723 ± 0.001

Table 2. Hammett (ρ_X)^a and Brönsted (β_X)^b Coefficients with X of the Reactions of **2** with X-Pyridines in DMSO at 85.0 °C

X \ Z		4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO, 4-Me, H	$-\rho_X$	1.43 ± 0.01	1.53 ± 0.01	1.55 ± 0.01	1.62 ± 0.01	1.67 ± 0.01
	β_X	0.31 ± 0.01	0.33 ± 0.01	0.34 ± 0.02	0.35 ± 0.01	0.36 ± 0.01
H, 3-MeO, 3-Cl	$-\rho_X$	0.60 ± 0.01	0.71 ± 0.01	0.77 ± 0.01	0.80 ± 0.01	0.86 ± 0.01
	β_X	0.09 ± 0.02	0.11 ± 0.03	0.12 ± 0.02	0.13 ± 0.03	0.14 ± 0.04

^aCorrelation coefficients, r, are better than 0.999. ^br ≥ 0.987.

Table 3. Hammett Coefficients (ρ_Z)^a with Z of the Reactions of **2** with X-Pyridines in DMSO at 85.0 °C

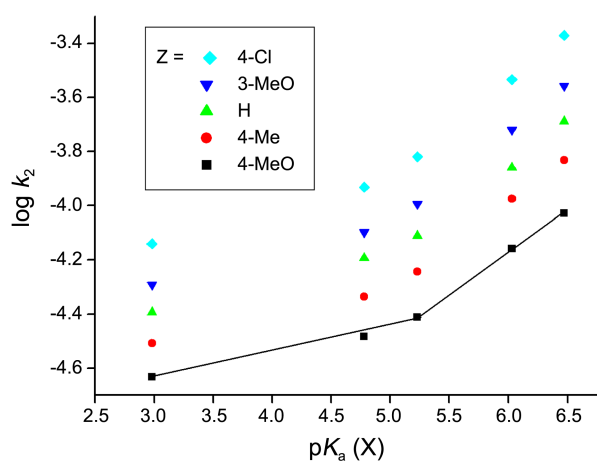
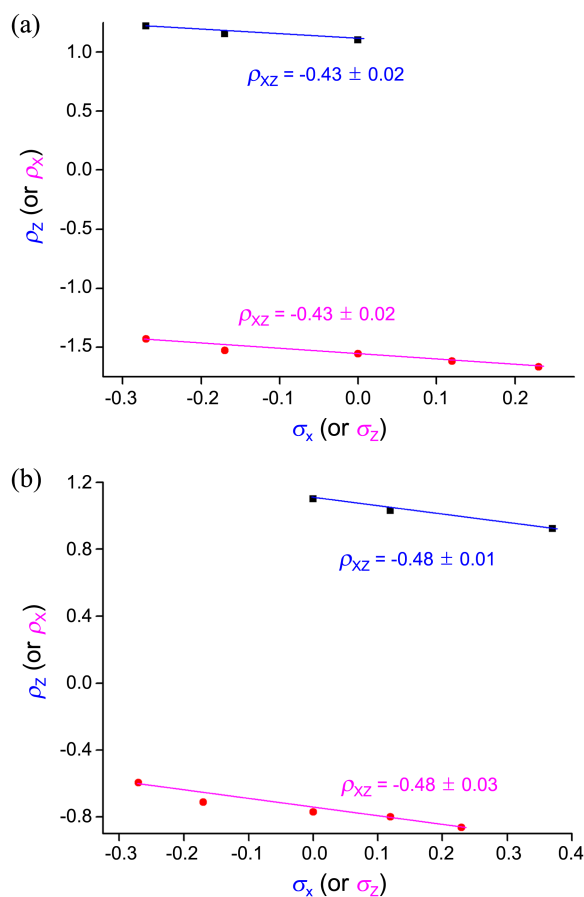
X	4-MeO	4-Me	H	3-MeO	3-Cl
ρ_Z	1.22 ± 0.04	1.15 ± 0.04	1.10 ± 0.03	1.03 ± 0.03	0.92 ± 0.03

^ar ≥ 0.988.

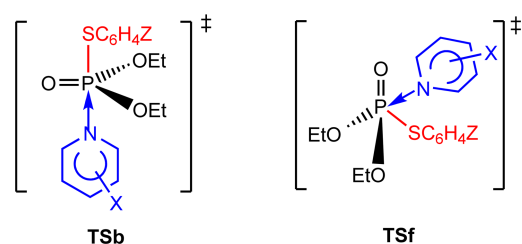
1) and Hammett (Fig. S1) plots for substituent X variations in the nucleophiles, however, exhibit biphasic concave upwards with a break point at X = H, while the Hammett plots (Fig. S2) for substituent Z variations in the leaving groups are linear. The magnitudes of the ρ_X and β_X values with the strongly basic pyridines are 2-3 times greater than those with the weakly basic pyridines. The ρ_X values consistently decrease (or more negative value; $\partial\rho_X < 0$) as the substituent Z becomes more electro-withdrawing ($\partial\sigma_Z > 0$), resulting in $\partial\rho_X/\partial\sigma_Z = (-)/(+) < 0$ for both the strongly and weakly basic pyridines. The ρ_Z values invariably decrease (or less positive value; $\partial\rho_Z < 0$) as the pyridine becomes less basic ($\partial\sigma_X > 0$), resulting in $\partial\rho_Z/\partial\sigma_X = (-)/(+) < 0$ for both the strongly and weakly basic pyridines (*vide infra*).

Figure 2 shows the two ρ_{XZ} values with the strongly (a) and weakly (b) basic pyridines, respectively, because the Hammett plots with X are biphasic. The cross-interaction constants (CICs; ρ_{XZ}) are obtained according to the definition as follows: $\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z$ and hence, $\rho_{XZ} = \partial^2\log(k_{XZ}/k_{HH})/\partial\sigma_X\partial\sigma_Z = \partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X$.² The sign of the ρ_{XZ} value is negative for both the strongly ($\rho_{XZ} = -0.43$) and weakly ($\rho_{XZ} = -0.48$) basic pyridines (*vide supra*). A concerted mechanism is proposed for both the strongly and weakly basic pyridines in spite of the biphasic concave upward free energy correlations for substituent X variations because the ρ_{XZ} has a negative value in a concerted S_N2 (or a stepwise mechanism with a rate-limiting bond formation) while a positive value in a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate.²

Biphasic concave upward free energy correlations with X can be substantiated by a change in the nucleophilic attack-

**Figure 1.** Brønsted plots with X of the reactions of **2** with X-pyridines in DMSO at 85.0 °C.**Figure 2.** Determination of ρ_{XZ} of the reactions of **2** with X-pyridines in DMSO at 85.0 °C. The obtained CICs by multiple regression are: (a) $\rho_{XZ} = -0.43 \pm 0.04$ ($r = 0.988$) with the strongly basic pyridines (X = 4-MeO, 4-Me, H); (b) $\rho_{XZ} = -0.48 \pm 0.03$ ($r = 0.988$) with the weakly basic pyridines (X = H, 3-MeO, 3-Cl).

ing direction towards the Z-thiophenoxide leaving group. A weakly basic group has a greater apicophilicity so that apical approach is favored for such nucleophiles.³ The apical nucleophilic attack should lead to a looser P–N bond in the TBP-5C structure because the apical bonds are longer than the equatorial bonds. Thus, greater magnitudes of the β_X ($= 0.31$ - 0.36) values with the strongly basic pyridines involving equatorial nucleophilic attack (*e.g.*, frontside attack TSf in Scheme 2) are obtained compared to those ($\beta_X = 0.09$ - 0.14) with the weakly basic pyridines involving apical nucleophilic attack (*e.g.*, backside attack TSb in Scheme 2). At a glance, the magnitudes of the ρ_{XZ} ($= -0.43$ and -0.48 with the strongly and weakly basic pyridines, respectively) values are not in line with the β_X ($= 0.31$ - 0.36 and 0.09 - 0.14 with the strongly and weakly basic pyridines, respectively) values because the magnitude of the ρ_{XZ} value is inversely proportional to the distance between X and Z through the reaction center.² This may be interpreted as follows: (i) the larger magnitudes of the β_X values with the strongly basic pyridines compared with those with the weakly basic pyridines indicate that the degree of bond formation with the strongly basic pyridines is greater than that with the weakly basic pyridines in the TS, as mentioned earlier; (ii) thus, the



Scheme 2. Backside apical attack TSb with the weakly basic pyridines and frontside equatorial attack TSf with the strongly basic pyridines.

comparable ρ_{XZ} ($\approx -0.45 \pm 0.03$) values with the strongly and weakly basic pyridines indicate that the degree of bond cleavage with the strongly basic pyridines is greater than that with the weakly basic pyridines in the TS; (iii) as a result, the tightness of the TS with the strongly basic pyridines is similar to that with the weakly basic pyridines, *i.e.*, the degrees of both bond formation and cleavage with the strongly basic pyridines are greater than those with the weakly basic pyridines; (iv) in other words, the β_X value only suggests the degree of bond formation while the ρ_{XZ} value suggests the sum of the degrees of both bond formation and cleavage in the TS; (v) and finally, the CIC is one of the strong tools to clarify the TS structure including both the degrees of bond formation and cleavage.

In general, the nonlinear free energy correlation of a concave upward plot is diagnostic of a change in the reaction mechanism where the reaction path is changed depending on the substituents, while nonlinear free energy correlation of the concave downward plot is diagnostic of a rate-limiting step change from bond breaking with the weakly basic nucleophiles to bond formation with the strongly basic nucleophiles.⁴ It is the suggestion of the authors that the biphasic concave upward free energy correlation is also diagnostic of a change in the nucleophilic attacking direction towards the leaving group from frontside with the strongly basic nucleophiles to backside with the weakly basic nucleophiles.

Table 4 summarizes the second-order rate constants in a given solvent at a given temperature, β_X and ρ_{XZ} values for the reactions of **1-3** with X-Pyridines. The pyridinolyses of **1** and **2** are conducted in DMSO at 85.0 °C because the rate is too slow to measure in MeCN even at 65.0 °C.⁵ It is well known that the displacement reaction rates of tetracoordinated phosphorus are mainly dependent upon the steric effects of the two ligands.⁶ Thus, the rate ratio of $k_2(\mathbf{1})/k_2(\mathbf{2}) = 7.1$ can be substantiated by greater steric congestion of diethoxy ligands compared to that of dimethoxy ligands in

Table 4. Summary of the Second-Order Rate Constants ($k_2 \times 10^3/\text{M}^{-1} \text{s}^{-1}$) with C₅H₅N, β_X and ρ_{XZ} for the Reactions of **1-3** with X-Pyridines

substrate	$k_2 \times 10^3$ (t/°C)	solvent	β_X	ρ_{XZ}
1: (MeO) ₂ P(=O)SC ₆ H ₄ Z	0.549 ^a (85.0)	DMSO	0.25-0.29/0.19-0.22 ^b	-0.35/-0.15 ^b
2: (EtO) ₂ P(=O)SC ₆ H ₄ Z	0.0774 ^a (85.0)	DMSO	0.31-0.36/0.09-0.14 ^b	-0.43/-0.48 ^b
3: (PhO) ₂ P(=O)SC ₆ H ₄ Z	44.2 ^a (35.0)	MeCN	0.88-0.93	-0.70/+0.76 ^c

^aZ = H. ^bStrongly/weakly basic pyridines. ^cZ = (4-Me, H)/(H, 4-Cl, 3-Cl).

Table 5. Activation Parameters for the Reactions of **1-3** (Z = H) with C₅H₅N

substrate	solvent	ΔH^\ddagger /kcal mol ⁻¹	$-\Delta S^\ddagger$ /cal mol ⁻¹ K ⁻¹
1: (MeO) ₂ P(=O)SPh	DMSO	19.8	18
2: (EtO) ₂ P(=O)SPh	DMSO	11.4	46
3: (PhO) ₂ P(=O)SPh	MeCN	2.1	58

the TS. However, neither steric effects nor inductive effects of diphenoxy ligands cannot rationalize exceptionally fast rate of **3**. The authors reported the exceptionally fast aminolysis rates of the chlorophosphates [(R₁O)(R₂O)P(=O)Cl-type] and chlorothiophosphates [(R₁O)(R₂O)P(=S)Cl-type] with phenoxy ligand(s), and suggested that the substrates with phenoxy ligand(s) are fully different from those with alkoxy ligands regarding the reactivity.^{5,7} The β_X values with **1** and **2** are relatively small compared to those with **3**. In view of the free energy correlations and sign of ρ_{XZ} , **1** and **2** exhibit biphasic concave upwards with X while linear with Z and show negative sign of ρ_{XZ} , indicating a concerted mechanism for both **1** and **2**.^{1a} On the contrary, **3** exhibits linear with X while biphasic concave downwards with Z and the sign of ρ_{XZ} is negative with electron-donating Z substituents while positive with electron-withdrawing Z substituents, indicating that the mechanism is changed from a rate-limiting bond formation with electron-donating Z substituents to a rate-limiting leaving group expulsion from the intermediate with electron-withdrawing Z substituents.^{1b}

Table 5 summarizes the activation parameters, enthalpies and entropies of activation, for the reactions of **1-3** (Z = H) with C₅H₅N in a given solvent and Table R1 lists the second-order rate constants and activation parameters for the reactions of **2** (Z = 4-MeO, H, 4-Cl) with C₅H₅N in DMSO.⁸ The authors reported that the small value of activation enthalpy ($\Delta H^\ddagger \approx 10$ kcal mol⁻¹) and large negative value of activation entropy ($\Delta S^\ddagger \approx -50$ cal mol⁻¹ K⁻¹) are typical for the aminolyses (pyridinolyses and anilinolyses) of the P=O (and P=S) systems regardless of the mechanism, concerted, stepwise with a rate-limiting bond making or stepwise with a rate-limiting bond breaking.⁷ However, the enthalpy of activation with **3** is considerably small while the enthalpy of activation and entropy of activation with **1** are exceptionally large and small negative value, respectively.⁹

Experimental Section

Materials. The substrates were prepared as reported earlier except Z = 3-MeO.¹⁰ The analytical and spectroscopic data

of *O,O*-diethyl *S*-3-methoxyphenyl phosphorothioate are given below (supporting information):

$(C_2H_5O)_2P(=O)SC_6H_4(3-OCH_3)$: Colorless oily liquid; 1H NMR (400 MHz, $CDCl_3$ & TMS), δ 1.26-1.30 (t, 6H), 3.77 (s, 3H), 4.12-4.19 (m, 4H), 6.86 (d, 1H, $J = 8.0$ Hz), 7.08-7.12 (t, 2H), 7.19-7.23 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ & TMS), δ 16.0, 55.4, 64.1, 115.0, 119.6, 126.6, 127.5, 130.0, 159.9; ^{31}P NMR (162 MHz, $CDCl_3$ & TMS), δ 28.2 (1P, s); GC-MS (EI, m/z) 276 (M^+).

Kinetic Procedure. The second-order rate constants and selectivity parameters were obtained as previously described.¹ The initial concentrations are as follows: [substrate] = 3.0×10^{-3} M and $[XC_5H_4N] = (0.10-0.30)$ M.

Product Analysis. *O,O*-Diethyl *S*-4-methylphenyl phosphorothioate and pyridine were reacted for more than 15 half-lives in DMSO at 85.0 °C. The product was extracted by ethyl acetate with several attempts. Solvent was removed under reduced pressure and gummy product was washed with diethyl ether for several times to remove excess pyridine. The analytical and spectroscopic data of the product are the following results (supporting information):

$[(C_2H_5O)_2P(=O)(NC_5H_5)]^+(4-CH_3C_6H_4S)^-$: Gummy semi-solid; 1H NMR (400 MHz, $DMSO-d_6$) δ 1.06-1.25 (t, 6H), 1.51-1.55 (s, 3H), 3.75-4.21 (m, 4H), 7.11 (d, 2H), 7.45 (d, 2H), 8.13-8.17 (t, 2H), 8.57-8.61 (t, 1H), 9.11-9.15 (d, 2H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 16.1, 56.3, 62.4, 124.9, 127.9, 128.1, 131.1, 131.2, 144.6, 145.3; ^{31}P NMR (162 MHz $DMSO-d_6$) δ -6.57 (1P s); LC-MS for $C_{16}H_{22}NO_3PS$ (m/z) 340 (M^+).

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- Table R1.** Second-Order Rate Constants and Activation Parameters for the Reactions of **2** ($Z = 4\text{-MeO, H, 4-Cl}$) with C_5H_5N in DMSO

Z	$k_2 \times 10^4 / M^{-1} s^{-1}$			$\Delta H^\ddagger /$ kcal mol ⁻¹	$-\Delta S^\ddagger /$ cal mol ⁻¹ K ⁻¹
	65.0 °C	75.0 °C	85.0 °C		
4-MeO	0.152 ± 0.001	0.247 ± 0.004	0.387 ± 0.002	10.5 ± 0.1	50 ± 1
H	0.282 ± 0.002	0.475 ± 0.001	0.774 ± 0.001	11.4 ± 0.1	46 ± 1
4-Cl	0.696 ± 0.001	1.01 ± 0.02	1.51 ± 0.01	8.7 ± 0.1	52 ± 1

- The small activation enthalpy of **3** might be attributed to ground state destabilization due to the two phenoxy ligands. The magnitudes of enthalpy and entropy of activation of **1** are largest and smallest, respectively, among the phosphoryl and thiophosphoryl transfer reactions studied in this lab.
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