

Kinetics and Mechanism of the Pyridinolysis of Diisopropyl Chlorothiophosphate in Acetonitrile

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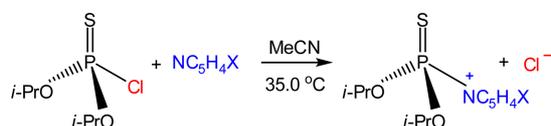
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The nucleophilic substitution reactions of diisopropyl chlorothiophosphate (**5**) with X-pyridines have been kinetically studied in MeCN at 35.0 °C. The Hammett and Brønsted plots for the substituent X variations in the nucleophiles show biphasic concave upwards with a break point at X = 3-Ph. The pyridinolysis rate of **5** exhibits great negative deviation from the Taft plot. A concerted S_N2 mechanism is proposed involving a change of the attacking direction of the X-pyridines from a frontside attack with the strongly basic pyridines to a backside attack with the weakly basic pyridines.

Key Words : Thiophosphoryl transfer reaction, Diisopropyl chlorothiophosphate, Pyridinolysis, Biphasic concave upward free energy relationship

Introduction

This lab previously reported the kinetics and mechanism of the pyridinolyses of the chlorothiophosphates in acetonitrile (MeCN): dimethyl [**1**: (MeO)₂P(=S)Cl],¹ diethyl [**2**: (EtO)₂P(=S)Cl],¹ dipropyl [**3**: (PrO)₂P(=S)Cl],² dibutyl [**4**: (BuO)₂P(=S)Cl],³ Y-aryl ethyl [**6**: (EtO)(YC₆H₄O)P(=S)Cl],⁴ and Y-aryl phenyl [**7**: (PhO)(YC₆H₄O)P(=S)Cl]⁵ chlorothiophosphates. To extend the kinetic studies on the pyridinolyses of the chlorothiophosphates, the nucleophilic substitution reactions of diisopropyl chlorothiophosphate (**5**) with X-pyridines are kinetically investigated in MeCN at 35.0 ± 0.1 °C (Scheme 1). The purpose of this work is to gain further systematic information into the reactivity, steric effects, and mechanism depending upon the variation of the two ligands (R₁O and R₂O) for the thiophosphoryl transfer reactions. The numbering of the substrates of **1-7** follows the sequence of the summation of the Taft steric constants of the two ligands, R₁ and R₂.⁶



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 pyridinolysis of diisopropyl chlorothiophosphate (**5**) in MeCN at 35.0 °C.

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 reaction, and the overall reaction is described by Scheme 1.

$$k_{\text{obsd}} = k_0 + k_2 [\text{XC}_5\text{H}_4\text{N}] \quad (1)$$

The second-order rate constants [k_2 (M⁻¹ s⁻¹)] are summarized in Table 1. The Brønsted β_X value was calculated by correlating $\log k_2(\text{MeCN})$ with $\text{p}K_{\text{a}}(\text{H}_2\text{O})$.⁷ This procedure of using $\text{p}K_{\text{a}}(\text{H}_2\text{O})$ instead of $\text{p}K_{\text{a}}(\text{MeCN})$ values of X-pyridines has been shown to be justified theoretically and experimentally.⁸ There is a practically constant difference between the two sets of $\text{p}K_{\text{a}}$ in H₂O and in MeCN for various X-pyridines so that the slopes in the two solvents differ insignificantly.⁸ 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 with a positive charge development at the nucleophilic N atom in the transition state (TS). However, both the Hammett ($\log k_2$ vs σ_X ; Fig. 1) and Brønsted [$\log k_2$ vs $\text{p}K_{\text{a}}(\text{X})$; Fig. 2] plots are biphasic concave upwards with a break point at X = 3-Ph. The magnitudes of ρ_X ($= -5.10 \pm 0.03$; $r = 0.999$) and β_X ($= 0.99 \pm 0.03$;

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/\text{M}^{-1} \text{s}^{-1}$) of the Reactions of Diisopropyl Chlorothiophosphate (**5**) with XC₅H₄N 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	122	32.4	11.0	4.60	2.50	2.32	1.35	1.34	1.02	0.880	0.832
$\times 10^4$	± 1	± 0.1	± 0.1	± 0.02	± 0.01	± 0.01	± 0.01	± 0.01	± 0.01	± 0.003	± 0.004

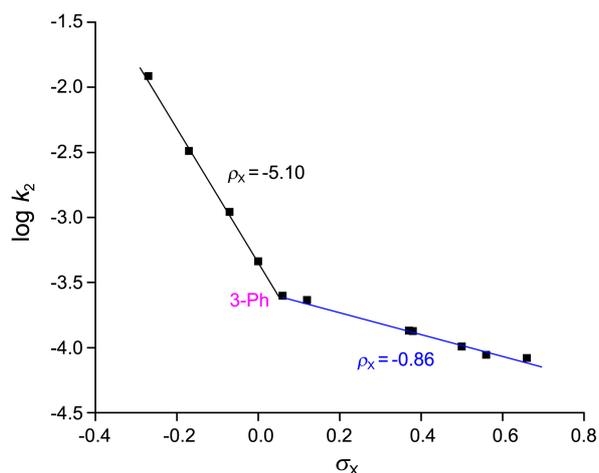


Figure 1. The Hammett plot ($\log k_2$ vs σ_X) of the reactions of diisopropyl chlorothiophosphate (**5**) with X-pyridines in MeCN at 35.0 °C.

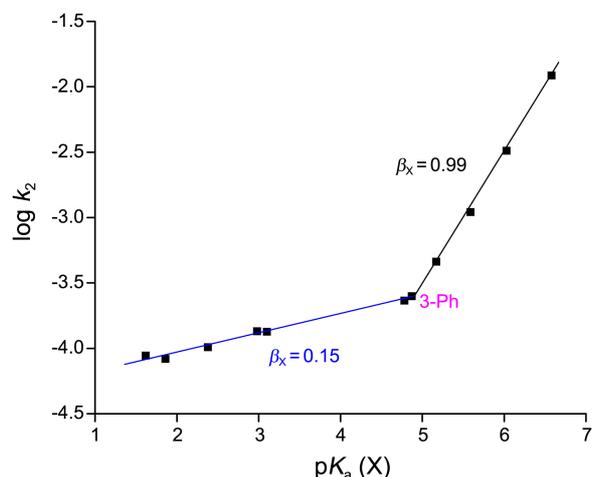


Figure 2. The Brønsted plot [$\log k_2$ vs $pK_a(X)$] of the reactions of diisopropyl chlorothiophosphate (**5**) with X-pyridines in MeCN at 35.0 °C.

$r = 0.999$) values with the strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph) are much (6-7 times) greater

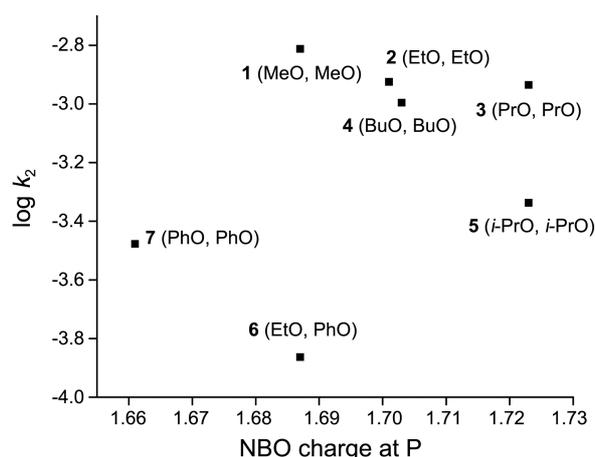


Figure 3. The plot of $\log k_2$ vs positive NBO charge at the P atom for the reactions of **1-7** with C_5H_5N in MeCN at 35.0 °C. The number of the substrate and two ligands are displayed next to the corresponding point.

than those [$\rho_X = -0.86 \pm 0.02$ ($r = 0.995$) and $\beta_X = 0.15 \pm 0.02$ ($r = 0.994$)] 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],⁹ summations of the Taft steric constants [$\Sigma E_S = E_S(R_1) + E_S(R_2)$] of the two ligands,⁶ Brønsted coefficients (β_X), cross-interaction constants (CICs; ρ_{XY}),¹⁰ and variation trends of the free energy relationships with X for the pyridinolyses of the seven chlorothiophosphates (**1-7**) in MeCN are summarized in Table 2.

There is no systematic consistency between the pyridinolysis rates and positive NBO charges at the reaction center P atom in the substrates as seen in Figure 3. For example, the NBO charge at P of **1** is the same as that of **6**, however, the pyridinolysis rate of **1** is fastest whereas that of **6** is slowest. It means that the positive charge of the reaction center P atom (or the inductive effects of the two ligands) does not play any role to determine the pyridinolysis rates of

Table 2. Summary of the Second-Order Rate Constants (k_2 with C_5H_5N at 35.0 °C), NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants (ΣE_S) of the Two Ligands, Brønsted Coefficients (β_X), CICs (ρ_{XY}), and Variation Trends of Free Energy Relationships with X for the Pyridinolyses of **1-7** in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-E_S^c$	β_X	ρ_{XY}	Trend
1: (MeO) ₂ P(=S)Cl	1.54	1.687	0	1.09/0.20 ^d	–	V ^f
2: (EtO) ₂ P(=S)Cl	1.19	1.701	0.14	1.02/0.29 ^d	–	V
3: (PrO) ₂ P(=S)Cl	1.16	1.723	0.72	1.08/0.31 ^d	–	V
4: (BuO) ₂ P(=S)Cl	1.01	1.703	0.78	1.26/0.31 ^d	–	V
5: (<i>i</i> -PrO) ₂ P(=S)Cl	0.460	1.723	0.94	0.99/0.15 ^d	–	V
6: (EtO)(YC ₆ H ₄ O)P(=S)Cl	0.137 ^b	1.687 ^b	2.55 ^b	2.31-2.33/0.45-0.47 ^d	0/0/0 ^e	V
7: (PhO)(YC ₆ H ₄ O)P(=S)Cl	0.333 ^b	1.661 ^b	4.96 ^b	1.36-1.50/0.23-0.48 ^d	2.42/5.14/–1.02/–0.04 ^e	V

^aSecond-order rate constant with unsubstituted pyridine (X = H) at 35.0 °C. ^bThe value with Y = H. ^cNote 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 $E_S(R_iO)$. ^dStrongly basic/weakly basic pyridines. ^eStronger nucleophiles and weaker electrophiles/weaker nucleophiles and weaker electrophiles/stronger nucleophiles and stronger electrophiles/weaker nucleophiles and stronger electrophiles. ^fThe symbol of V indicates biphasic concave upward free energy relationship with a break point for the substituent X variations in the nucleophiles.

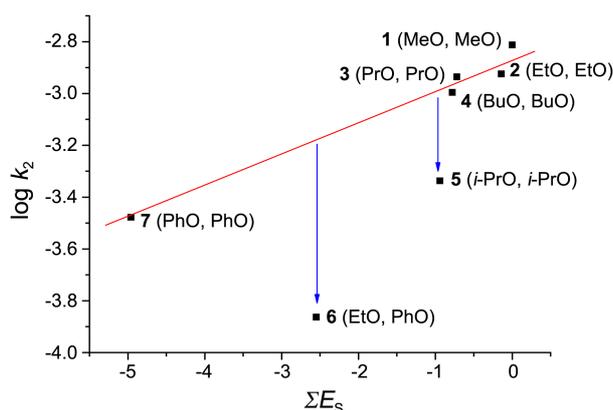


Figure 4. The Taft plot of $\log k_2$ vs ΣE_s for the reactions of **1-7** with C_5H_5N in MeCN at $35.0\text{ }^\circ\text{C}$. The number of the substrate and two ligands are displayed next to the corresponding point.

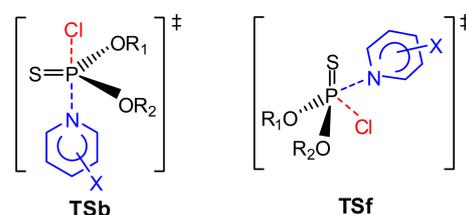
chlorothiophosphates.

The sequence of the pyridinolysis rates of **1-7**, when excluding **5** and **6**, is inversely proportional to the summation of the Taft steric constants (or size) of the two ligands (R_1O and R_2O); the greater the size of the two ligands, the rate becomes slower. These results indicate that the steric effects play an important role over the inductive effects of the two ligands to determine the pyridinolysis rates of the chlorothiophosphates. The Taft eq., ' $\log k_2 = \delta \Sigma E_s + C$ ', can be used to rationalize the steric effect of the two ligands on the reaction rate, where k_2 is the second-order rate constant with unsubstituted pyridine in MeCN at $35.0\text{ }^\circ\text{C}$, E_s is the Taft steric constant [$E_s(R) = 0(\text{Me}); -0.07(\text{Et}); -0.36(\text{Pr}); -0.39(\text{Bu}); -0.47(i\text{-Pr}); -2.48(\text{Ph})$], ΣE_s is the summation of the steric constants of the two ligands, and δ is the sensitivity coefficient.⁶ Herein, ' $\Sigma E_s = E_s(R_1) + E_s(R_2)$ ' is introduced instead of ' $\Sigma E_s = E_s(R_1O) + E_s(R_2O)$ ' since the data of $E_s(R_1O)$ is not available. Figure 4 shows the Taft plot of $\log k_2$ with unsubstituted pyridine (C_5H_5N) against the summation of the Taft steric constants of the two ligands for the pyridinolyses of seven chlorothiophosphates (**1-7**) in MeCN at $35.0\text{ }^\circ\text{C}$, giving the sensitivity coefficient of $\delta = 0.12$ ($r = 0.989$) with five substrates of **1-4** and **7**. The pyridinolysis rates of **5** and **6** exhibit great negative deviations from the Taft plot.

The anilinolysis rates with $C_6H_5NH_2$ of the chlorothiophosphates (**1-7**) in MeCN at $55.0\text{ }^\circ\text{C}$ are roughly dependent upon the steric effects over the inductive effects of the two ligands, giving the sensitivity coefficients of $\delta = 0.16$ ($r = 0.879$) with six substrates of **1-4**, **6**, and **7** (see Fig. R1).¹¹ The anilinolysis rate of **5** with the two *i*-PrO ligands exhibits great negative deviation from the Taft plot, as observed in the pyridinolysis rate of **5**. The anilinolysis¹² and pyridinolysis¹³ rates of diisopropyl chlorophosphate [$(i\text{-PrO})_2P(=O)Cl$; P=O counterpart of **5**] with the two *i*-PrO ligands in MeCN also exhibited great negative deviations from the Taft plot. The substrate of **5** has not only the greatest magnitude of the positive NBO charge at the reaction center P atom among seven chlorothiophosphates but also considerably smaller size of the two ligands compared to **7**. These indicate that the

aminolysis (anilinolysis and pyridinolysis) rate of **5** is exceptionally slow to be rationalized by the conventional stereoelectronic effects. At this point, the authors tentatively suggest that the exceptionally slow rate of the aminolysis (anilinolysis and pyridinolysis) of **5** is attributed to an unexpected steric hindrance of the two *i*-PrO ligands which cannot be predicted by the Taft ΣE_s . The great negative deviation of the pyridinolysis rate of **6** from the Taft plot is very unusual: the anilinolysis rate of **6** (see Fig. R1),^{11b} and the pyridinolysis¹⁴ and anilinolysis^{11b} rates of phenyl ethyl chlorophosphate [$(\text{EtO})(\text{PhO})P(=O)Cl$; P=O counterpart of **6**] showed only a little deviations from the Taft plots.

As seen in Table 2, the free energy relationships with X are all biphasic concave upwards. The β_X values of **1-5** are similar: $\beta_X = 1.0\text{-}1.3$ with the strongly basic pyridines and $\beta_X = 0.2\text{-}0.3$ with the weakly basic pyridines, strongly suggesting the same reaction mechanisms of the pyridinolyses of **1-5**. The β_X (≈ 2.3) value of **6** 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. The β_X ($= 1.4\text{-}1.5$) values of **7** with the strongly basic pyridines are relatively large. The β_X values of **6** and **7** with the weakly basic pyridines are somewhat greater than those of **1-5**. The Hammett plots of **6** for the substituent Y variations in the substrates are biphasic concave upwards with a break (minimum) point at $Y = H$ while those of **7** are concave downwards with a break point at $Y = H$. Thus, the four values of CICs, ρ_{XY} , were obtained for both **6** and **7**. In **6**, 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 TS, in which the reaction proceeds through a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate.¹⁵ 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 **7**, a stepwise process was proposed involving a rate-limiting step change from bond breaking with the weaker electrophiles based on the



Scheme 2. Backside attack TSb and frontside attack TSf.

Table 3. Activation Parameters^a for the Reaction of Diisopropyl Chlorothiophosphate (**5**) with Pyridine (C₅H₅N) in MeCN

<i>t</i> /°C	<i>k</i> ₂ × 10 ⁴ /M ⁻¹ s ⁻¹	Δ <i>H</i> [‡] /kcal mol ⁻¹	-Δ <i>S</i> [‡] /cal mol ⁻¹ K ⁻¹
35.0	4.60 ± 0.02		
40.0	7.00 ± 0.03	15.2 ± 0.4	25 ± 1
45.0	10.6 ± 0.1		

^aCalculated by the Eyring eq.

large positive ρ_{XY} value to bond formation with the stronger electrophiles based on the negative ρ_{XY} value.¹⁶ The non-linear 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 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 **1-4**.

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 non-linear 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.¹⁷ It is the suggestion of the authors that the concave upward Hammett and Brønsted 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.^{1,4,5,13,18}

Activation parameters, enthalpy and entropy of activation, are determined for the pyridinolysis (with C₅H₅N) of **5** in Table 3. The enthalpy of activation is relatively larger (15.2 kcal mol⁻¹) and entropy of activation is relatively smaller negative values (-25 cal mol⁻¹ K⁻¹) compared to the typical aminolyses of P=S systems.

Experimental Section

Materials. GR grade X-pyridines and HPLC grade MeCN (water content is less than 0.005%) were used for kinetic studies without further purification. Diisopropyl chlorothiophosphate (**5**) was prepared as described previously.^{11f}

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

[XC₅H₄N] = (0.10-0.30) M. The second-order rate constants, *k*₂, were obtained from the slope of a plot of *k*_{obsd} vs [X-pyridine] with at least five concentrations of pyridine. The pseudo-first-order rate constant values (*k*_{obsd}) were the average of at least three runs that were reproducible within ± 3%.

Product Analysis. Diisopropyl chlorothiophosphate (**5**) was reacted with excess pyridine, for more than 15 half-lives at 35.0 °C in MeCN. Solvent 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 (see Supporting Information):

[(*i*-PrO)₂P(=S)NC₅H₅]⁺Cl⁻: Brown liquid; ¹H NMR (400 MHz, CDCl₃) δ 1.17-1.38 (12H, m, 4CH₃, *i*-Pr), 3.78-3.85 (2H, m, 2OCH, *i*-PrO), 7.96-8.00 (2H, t, *J* = 6.8 Hz, pyridinium), 8.43-8.47 (1H, t, *J* = 7.2 Hz, pyridinium), 8.88-8.89 (2H, d, *J* = 5.2 Hz, pyridinium); ¹³C NMR (100 MHz, CDCl₃) δ 23.66-23.95 (4CH₃, *i*-Pr), 55.22 (2OCH, *i*-PrO), 113.56, 126.77, 132.86, 142.11, 144.81 (C=C, pyridinium); ³¹P NMR (162 MHz, CDCl₃) δ 64.77 (s, 1P, P=S); MS (ESI) *m/z*, 296 (M⁺).

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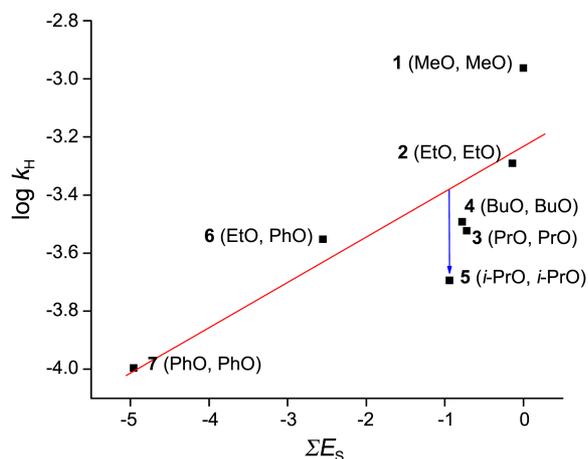


Figure R1. The Taft plot of $\log k_H$ vs ΣE_S for the reactions of **1-7** with $C_6H_5NH_2$ in MeCN at 55.0 °C. The substrate of **5** shows great negative deviation from the Taft plot. The sensitivity coefficient of $\delta = 0.16$ ($r = 0.879$) is obtained with six substrates of **1-4**, **6**, and **7**.

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15. The value of ρ_{XY} could be null when the X and Y are too far apart to interact each other. The observed $\rho_{XY} = 0$ with four blocks is the very special.
16. In general, the negative sign of ρ_{XY} implies that the reaction proceeds through a concerted mechanism, while a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate with the positive sign of ρ_{XY} , and the magnitude of ρ_{XY} value is inversely proportional to the distance between X and Y through the reaction center.
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