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Pyridinolysis of Diethyl Phosphinic Chloride in Acetonitrile

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Nucleophilic substitution on P=O (and P=S) center is not only important in biochemistry and is also extensive in synthesis and organometallic chemistry. The authors reported various types of phosphoryl transfer reactions to clarify the mechanism.[1] Herein, the reactions of diethyl phosphinic chloride (**2O**) with substituted pyridines are investigated kinetically in acetonitrile at 45.0 ± 0.1 °C to gain further information of mechanism. The pyridinolyses of eleven $R_1R_2P(=O$ or $S)Cl$-type substrates in MeCN (eq 1) are reviewed to obtain systematic information on phosphoryl transfer reaction mechanism. The kinetic results are discussed on the bases of thio effect on reactivity, steric effect of R_1 and R_2 on reactivity of substrate, electrophilicity of substrate, comparison between anilinolysis and pyridinolysis, and pyridinolysis mechanism. Eleven $R_1R_2P(=O$ or $S)Cl$-type substrates are as follows: dimethyl phosphinic chloride (**1O**);[1h] dimethyl thiophosphinic chloride (**1S**);[1h] diethyl phosphinic chloride (**2O**); dimethyl chlorophosphate (**3O**);[1g] dimethyl chlorothiophosphate (**3S**);[1g] diethyl chlorophosphate (**4O**);[1g] diethyl chlorothiophosphate (**4S**);[1g] diphenyl phosphinic chloride (**5O**);[1d] diphenyl thiophosphinic chloride (**5S**);[1d] Y-*O*-aryl phenyl phosphonochloridothioates (**6S**);[1f] Y-aryl phenyl chlorophosphates (**7O**).[1a] The numbering of the substrates (**1-7**) follows the sequence of the size of the two ligands ($R_1 + R_2$), and **O** and **S** represent the P=O and P=S systems, respectively.

$$R_1R_2P(=O \text{ or } S)Cl + XC_5H_4N \xrightarrow{MeCN} R_1R_2P(=O \text{ or } S)\overset{+}{N}C_5H_4X + \overset{-}{Cl} \quad (1)$$

$(CH_3)_2P(=O)Cl$ (**1O**); $(CH_3)_2P(=S)Cl$ (**1S**); $(C_2H_5)_2P(=O)Cl$ (**2O**); $(CH_3O)_2P(=O)Cl$(**3O**); $(CH_3O)_2P(=S)Cl$ (**3S**); $(C_2H_5O)_2P(=O)Cl$ (**4O**); $(C_2H_5O)_2P(=S)Cl$ (**4S**); $(C_6H_5)_2P(=O)Cl$ (**5O**); $(C_6H_5)_2P(=S)Cl$ (**5S**); $(YC_6H_4O)(C_6H_5)P(=S)Cl$ (**6S**); $(YC_6H_4O)(C_6H_5O)P(=O)Cl$ (**7O**)

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq 2 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. The second-order rate constants (k_2) were determined for at least five concentrations of anilines. The linear plots of eq 2 suggest that there is no base-catalysis or noticeable side reactions and that the overall reaction is described by eq 1.

$$k_{obsd} = k_0 + k_2[XC_5H_4N] \quad (2)$$

The k_2 values are summarized in Table 1. The substituent effects of the nucleophiles upon the pyridinolysis rates correlate with those for a typical nucleophilic substitution reaction with negative ρ_X and positive β_X value. The Brönsted β_X value was obtained by correlating log k_2(MeCN) with pK_a(H_2O),[2] which was justified theoretically and experimentally.[3] Both the Hammett (logk_2 *vs* σ_X) and Brönsted [log k_2 *vs* pK_a(X)] plots are linear with $\rho_X = -2.52 \pm 0.08$ (r = 0.996) and $\beta_X = 0.45 \pm 0.02$ (r = 0.994).

Table 2 shows the summations of inductive effects of the two ligands [$\sum\sigma_I = \sigma_I(R_1) + \sigma_I(R_2)$],[4] natural bond order (NBO) charges on the P atom reaction center in the gas phase [B3LYP/6-311+G(d,p) level of theory],[1n] summations of steric parameters of the two ligands [$\sum E_S = E_S(R_1) + E_S(R_2)$],[5] second-order rate constants (k_2) at 35.0 °C, and Brönsted coefficients (β_X) and cross-interaction constants (CICs; ρ_{XY})[6] for the pyridinolyses of eleven $R_1R_2P(=L)Cl$-type in MeCN. The arrangement of the substrates in the column for P=O (**1O-7O**) and P=S (**1S-6S**) systems follows the sequence of the degree of steric hindrance (i.e., bulkiness) of the two ligands.

The P=O systems are 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 that favors O over S.[7] The NBO charges on the P atom of P=O systems are greater (*ca*. 0.5 - 0.6) than those of their P=S counterparts, implying the electronegativity difference between O and S. Herein, the pyridinolysis rate ratios of P=O and their P=S counterparts of $R_1R_2P(=O$ or $S)Cl$ type in MeCN at 35.0 °C are great as follows: k_2(**1O**)/k_2(**1S**) = 137,000; k_2(**3O**)/k_2(**3S**) = 42; k_2(**4O**)/k_2(**4S**) = 44; k_2(**5O**)/k_2(**5S**) = 30. The correlation $\sum\sigma_I$ with the NBO charge on the P atom reaction center is roughly linear. The plots of the NBO charge on P against $\sum\sigma_I$ yield the slopes of 0.622 (r = 0.946) and 0.846 (r = 0.918) for P=O and P=S systems, respectively. The sequence of the second-order

Table 1. Second-Order Rate Constants ($k_2 \times 10^2$/M^{-1} s^{-1}) of the Reactions of $Et_2P(=O)Cl$ (**2O**) with XC_5H_4N in MeCN at 45.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
$k_2 \times 10^2$	96.1 ± 2.3	49.9 ± 1.4	27.1 ± 0.3	18.8 ± 0.4	11.0 ± 0.3	8.29 ± 0.05	2.00 ± 0.04	1.94 ± 0.05	1.27 ± 0.02	0.500 ± 0.012	0.498 ± 0.019

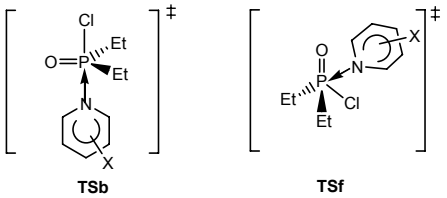
Table 2. Summary of Summations of Inductive Effects of the Two Ligands ($\sum\sigma_I$), NBO Charges on Reaction Center P, Summations of Steric Parameters of the Two Ligands ($\sum E_S$), Second-Order Rate Constants (k_2) at 35.0 °C, and Selectivity Parameters (β_X and ρ_{XY}) for the Pyridinolyses of Eleven R_1R_2P(=O or S)Cl-type in MeCN

sub.	R_1	R_2	$\sum\sigma_I$	charge on P	$-\sum E_S$	$k_2 \times 10^{3a}$	β_X	ρ_{XY}	ref.
1O	Me	Me	−0.02	1.793	0.00	102,000[b]	0.17[g]/−0.03[h]	-	1h
2O	Et	Et	−0.02	1.817	0.14	127[c]	0.45	-	this work
3O	MeO	MeO	0.60	2.226	-	64.7	0.63	-	1g
4O	EtO	EtO	0.56	2.236	-	52.8	0.73	-	1g
5O	Ph	Ph	0.24	1.844	4.96	54.6	0.68	-	1d
7O	YC_6H_4O	PhO	0.80	2.230	-	266[d]	0.16 - 0.18	−0.15	1a
1S	Me	Me	−0.02	1.180	0.00	0.744	0.97[i]/0.27[j]	-	1h
3S	MeO	MeO	0.60	1.687	-	1.54[e]	1.09[g]/0.20[h]	-	1g
4S	EtO	EtO	0.56	1.701	-	1.19[f]	1.02[g]/0.29[h]	-	1g
5S	Ph	Ph	0.24	1.236	4.96	1.83	1.53[g]/0.38[h]	-	1d
6S	YC_6H_4O	Ph	0.52	1.462	-	11.4	0.87 - 0.95	−0.46	1f

[a]For the reactions of X = H in nucleophiles, and Y = H in substrates (for **7O** and **6S**) at 35.0 °C. [b]Extrapolated value in the Arrhenius plot with kinetic data: k_2 = 34,300, 40,400, and 53,900 × 10^{-3} M^{-1} s^{-1} at −25.0, −15.0, and −5.0 °C, respectively. [c]Experimental value. [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. [e]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. [f]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. [g]For X = 4-MeO, 4-Me, 3-Me, H, and 3-Ph. [h]For X = 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, and 4-CN. [i]For X = 4-MeO, 4-Me, 3-Me, and H. [j]For X = H, 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, and 4-CN.

rate constants of the pyridinolyses for both the P=O and P=S systems does not show systematic consistency with $\sum\sigma_I$, NBO charge on P, or even $\sum E_S$. These results indicate that the pyridinolysis rates of R_1R_2P(=L)Cl in MeCN are not dependent upon one dominant factor but on many factors.

The pyridinolyses of **1O**, **1S**, **3S**, **4S**, and **5S** yield biphasic concave upward free energy correlation (Hammett and Brönsted plots) for substituent X variations with greater and smaller magnitudes of slopes for weakly and strongly basic nucleophiles, respectively.[8] The authors proposed a concerted mechanism with a dominant backside nucleophilic attack towards the Cl leaving group (TSb) for weakly basic pyridines, and a concerted mechanism with a dominant frontside nucleophilic attack (TSf) for strongly 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 for weakly basic pyridines and greater values for strongly basic pyridines.



TSb **TSf**

The greater β_X value for the more basic pyridines suggests a dominant frontside attack with greater bond formation compared to a dominant backside attack for the 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,9] Since apical bonds are longer than equatorial bonds,[1b,9a] 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] Biphasic concave upward Hammett and Brönsted plots for substituent X variations in the nucleophiles of the reactions of Y-aryl phenyl isothiocyanophosphate with X-pyridines in MeCN was also interpreted as a change in the nucleophilic attacking direction from dominant backside for less basic pyridines (β_X = 0.12 - 0.15) to dominant frontside for more basic pyridines (β_X = 1.13 - 1.28).[1c] 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.

The S_N2 reaction mechanisms were proposed for the pyridinolyses of both **7O** and **6S** on the basis of the negative sign of the CIC, ρ_{XY}.[6] A relatively small degree of bond formation in the early TS could be proposed for **7O** on the basis of the small magnitudes of ρ_{XY} and β_X,[1a] while a relatively large degree of bond formation in the TS could be proposed for **6S** on the basis of the large magnitudes of ρ_{XY} and β_X.[1f]

In the pyridinolysis of **3O** (β_X = 0.63), **4O** (β_X = 0.73), and **5O** (β_X = 0.68), the authors proposed a concerted mechanism with both frontside and backside attacks, and the fraction of a frontside attack is more or less larger than that of a backside attack, on the basis of the magnitudes of β_X values. Taking into account β_X = 0.17 of **1O** for weakly basic pyridines where the reaction proceeds through frontside nucleophilic attack, the authors propose a concerted mechanism with greater fraction of a frontside attack than that of a backside attack for the pyridinolysis of **2O** with β_X = 0.445. Both front and backside nucleophilic attack were observed in the anilinolyses of some R_1R_2P(=L)Cl-type in MeCN.[1c-t]

As seen in Table 3, predominant factor to determine the anilinolysis rates of R_1R_2P(=L)Cl in MeCN is the degree of steric hindrance, since the anilinolysis rates are inversely proportional to the size of the two ligands ($\sum E_S$). The steric effects of the two ligands (R_1 and R_2) on the anilinolysis rates of P=O

Table 3. Second-Order Rate Constants (k_{Py} and $k_{An} \times 10^3/M^{-1} s^{-1}$) of the Pyridinolysis ($C_5H_5N$) at 35.0 °C and Anilinolysis ($C_6H_5NH_2$) at 55.0 °C, and Rate Ratios [k_{Py}(35.0 °C)/k_{An}(55.0 °C)] of Ten R_1R_2P(=O or S) Cl-type in MeCN

sub.	R_1	R_2	$k_{Py} \times 10^3$ (35.0 °C)	$k_{An} \times 10^3$ (55.0 °C)	k_{Py}(35.0 °C)/ k_{An}(55.0 °C)	ref.
1O	Me	Me	102,000	7,820	13	1h,[a] 1r[b]
2O	Et	Et	127	189	0.67	this work,1u
3O	MeO	MeO	64.7	4.28	15	1g, 1p
4O	EtO	EtO	52.8	2.82	19	1g, 1p
5O	Ph	Ph	54.6	1.73	32	1d, 1m
7O	PhO	PhO	266	0.891	299	1a, 1j
1S	Me	Me	0.744	9.79	0.076	1h, 1s
3S	MeO	MeO	1.54	1.09	1.4	1g, 1p
4S	EtO	EtO	1.19	0.512	2.3	1g, 1p
5S	Ph	Ph	1.83	0.601	3.0	1d, 1n

[a]Pyridinolysis. [b]Anilinolysis.

are much greater than those of P=S systems: k_{An} (**1O** with two small Me)/k_{An} (**5O** with two large Ph) = 4,520 for P=O, while k_{An} (**1S** with two small Me)/k_{An} (**5S** with two large Ph) = 16 for P=S system in MeCN at 55.0 °C. The approach of the aniline nucleophile to the reaction center P should cause extensive steric hindrance when the attacking and leaving groups occupy apical positions in a TBP-5C TS of a backside attack, because of not only a relatively large size of the aniline nucleophile, but also the orientation restriction of the attacking aniline. The lone pair of the amino nitrogen is sp^3-type, thus the angle of C (α-carbon of phenyl ring)-N (amino nitrogen)-P (reaction center of substrate) would be > 109.5° in the TS. The degree of steric hindrance would thus be greater as the ligands of R_1 and R_2 become bulkier in the TS. In contrast, the pyridine ring, located more or less parallel to the attacking axis in the TBP-5C TS, would experience much less steric congestion compared to the phenyl ring of the aniline.

The pyridinolysis rate is usually rather faster than the anilinolysis rate for both P=O and P=S systems (except for **1S**),[10] even taking into account the greater basicity of pyridine than aniline [pK_a (aniline) = 10.56 and pK_a (pyridine) = 12.33 in MeCN;[11] pK_a (aniline) = 4.60[12] and pK_a (pyridine) = 5.17 in water at 25.0 °C]. The rate ratio of k_{Py} (35.0 °C)/k_{An} (55.0 °C) increases as the size of the two ligands increases for both P=O and P=S system. However, the rate ratios for P=O are much greater than those for P=S systems.

In summary, the pyridinolysis of diethyl phosphinic chloride (**2O**) is investigated kinetically in acetonitrile at 45.0 °C. The authors propose a concerted mechanism with greater fraction of a frontside attack than that of a backside attack for the pyridinolysis of **2O**. The pyridinolyses of eleven R_1R_2P(=O or S)Cl-type substrates in MeCN (eq 1) are reviewed to obtain systematic information on phosphoryl transfer reaction mechanism. The pyridinolysis rates of R_1R_2P(=O or S)Cl-type substrates are not dependent upon one dominant factor but on many factors, while the anilinolysis rates of R_1R_2P(=O or S)Cl-type substrates are predominantly dependent upon the steric effects of two ligands, R_1 and R_2.

Experimental Section

Materals. GR grade diethyl phosphinic chloride (**2O**) (min 97%) was used without further purification. GR grade pyridines were used without further purification. HPLC grade acetonitrile (less than 0.005% water content) was used without further purification.

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 as previously described[1a-i] using large excesses of nucleophiles, [**2O**] = 0.001 M and [XC_5H_4N] = 0.01 - 0.08 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 phosphinic chloride was reacted with excess pyridine for more than 15 half-lives at 45.0 °C in acetonitrile. The insoluble products were washed several times with diethyl ether and isolated. The solvent was removed under reduced pressure. Analytical data of the products gave the following results:

$(C_2H_5)_2P(=O)\ N^+C_5H_5Cl^-$. White gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10, 1.12, 1.14, 1.15, 1.17, 1.19 (6H, m, CH_3), 1.72, 1.74, 1.75, 1.77 (4H, m, CH_2), 7.26, 7.98, 8.00, 8.01, 8.02, 8.47, 8.91, 8.92, 8.93 (5H, m, pyridine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.64, 5.69 (CH_3), 20.41, 21.34 (CH_2), 127.11, 141.18, 145.57, 149.45 (C=C, pyridine); ^{31}P NMR (162 MHz, $CDCl_3$) δ 67.75 (1P, s, P=O); *m*/*z*, 217 (M^+); Anal. Calcd for $C_9H_{15}ClNOP$: C, 49.21; H, 6.88; N, 6.38. Found: C, 49.15; H, 7.05; N, 6.52.

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