

Kinetics and Mechanism of the Pyridinolyses of Dimethyl Phosphinic and Thiophosphinic Chlorides in Acetonitrile

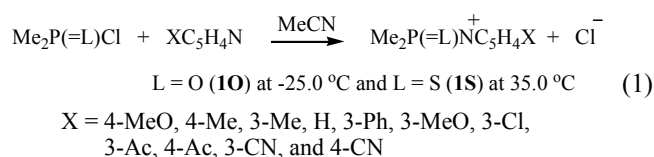
Nilay Kumar Dey, Keshab Kumar Adhikary, Chan Kyung Kim,* and Hai Whang Lee*

Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr

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Continuing the studies on phosphoryl transfer reactions,¹ the reactions of dimethyl phosphinic [Me₂P(=O)Cl; **1O**] and thiophosphinic [Me₂P(=S)Cl; **1S**] chlorides with substituted (X) pyridines are investigated kinetically in acetonitrile (MeCN) at -25.0 and 35.0 °C, respectively (eq 1) to clarify the phosphoryl transfer mechanism, as well as to compare the pyridinolyses of diphenyl phosphinic [Ph₂P(=O)Cl; **2O**] and thiophosphinic [Ph₂P(=S)Cl; **2S**] chlorides.^{1d}



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.

$$k_{\text{obsd}} = k_0 + k_2 [\text{XC}_5\text{H}_4\text{N}] \quad (2)$$

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 X-pyridines. 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. The k_2 values and the selectivity parameters (ρ_X and β_X) are summarized in Table 1. The pyridinolysis rates of **1O** are surprisingly faster than those of **1S** (note the reaction temperature and order of magnitude of second-order rate constant: -25.0 °C and +35.0 °C; 10^1 and 10^{-4} for **1O** and **1S**, respectively). The substituent effects of the nucleophiles upon the pyridinolysis rates of **1S** correlate with those for a typical nucleophilic substitution reaction, whereby a stronger nucleophile results in a faster rate. However, those of **1O** are not consistent with a typical one, in which unusual *minimum* rate is obtained at 3-methoxy pyridine. As a result, both negative ρ_X ($= -0.87$) and *positive* ρ_X ($= +0.16$) values are observed for strongly and weakly basic pyridines, respectively. The Brønsted β_X values were obtained by correlating $\log k_2$ (MeCN) with $\text{p}K_a$ (H₂O), which was justified theoretically and experimentally.²

As seen in Figure 3 (and Table 1), the pyridinolysis (C₅H₅N) rate constant of the P=O system is greater than that of its P=S counterpart: $k_2(\mathbf{1O})/k_2(\mathbf{1S}) = 10.2 \times 10^1/7.44 \times 10^{-4} = 137,000$

Table 1. Second-order rate constants ($k_2/\text{M}^{-1} \text{s}^{-1}$) and selectivity parameters^a (ρ_X and β_X) for the reactions of dimethyl phosphinic (**1O**) and thiophosphinic (**1S**) chlorides with XC₅H₄N in MeCN at -25.0 and 35.0 °C, respectively

X	$k_2 \times 10^{-1}$ (-25.0 °C) 1O [Me ₂ P(=O)Cl]	$k_2 \times 10^4$ (35.0 °C) 1S [Me ₂ P(=S)Cl]
4-MeO	5.89 ± 0.17	172 ± 4
4-Me	4.85 ± 0.10	50.6 ± 1.2
3-Me	4.05 ± 0.12	18.8 ± 0.2
H	3.43 ± 0.04	7.44 ± 0.14
3-Ph	3.03 ± 0.09	6.13 ± 0.13
3-MeO	2.79 ± 0.03	4.77 ± 0.14
3-Cl	3.06 ± 0.03	1.98 ± 0.01
3-Ac	3.08 ± 0.05	1.91 ± 0.01
4-Ac	3.22 ± 0.07	1.07 ± 0.02
3-CN	3.31 ± 0.09	0.797 ± 0.022
4-CN	3.44 ± 0.10	0.734 ± 0.012
ρ_X	-0.87 ± 0.02 (r = 0.999) ^b +0.16 ± 0.01 (r = 0.988) ^c	-4.96 ± 0.18 (r = 0.999) ^d -1.62 ± 0.06 (r = 0.995) ^e
β_X	+0.17 ± 0.01 (r = 0.999) ^b -0.03 ± 0.01 (r = 0.989) ^c	+0.97 ± 0.01 (r = 0.999) ^d +0.27 ± 0.02 (r = 0.990) ^e

^aThe σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. The $\text{p}K_a$ values were taken from (i) Fischer, A.; Galloway, W. J.; Vaughan, J. J. *Chem. Soc.* **1964**, 3591; (ii) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; Chapter 8. ^bFor X = 4-MeO, 4-Me, 3-Me, H, and 3-Ph. ^cFor X = 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, and 4-CN. ^dFor X = 4-MeO, 4-Me, 3-Me, and H. ^eFor X = H, 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, and 4-CN.

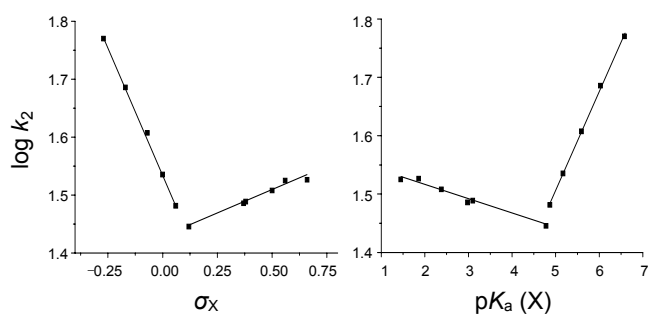


Figure 1. The Hammett ($\log k_2$ vs σ_X) and Brønsted [$\log k_2$ vs $\text{p}K_a(\text{X})$] plots of the reactions of **1O** [Me₂P(=O)Cl] with X-pyridines in MeCN at -25.0 °C.

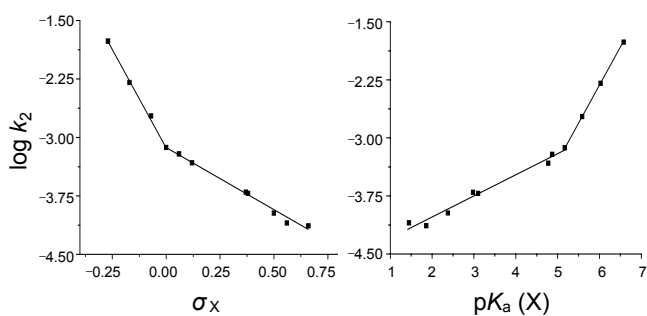


Figure 2. The Hammett ($\log k_2$ vs σ_X) and Brønsted [$\log k_2$ vs $pK_a(X)$] plots of the reactions of **1S** [$\text{Me}_2\text{P}(=\text{S})\text{Cl}$] with X-pyridines in MeCN at 35.0 °C.

and $k_2(\mathbf{2O})/k_2(\mathbf{2S}) = 30$.^{1d} Herein, the second-order rate constant, $k_2 = 10.2 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$, at 35.0 °C for the reactions of **1O** with unsubstituted pyridine was obtained by extrapolation in the Arrhenius plot with the empirical kinetic data ($r = 0.984$): $k_2 = 3.43$ (–25.0 °C), 4.04 (–15.0 °C), and $5.39 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$ (–5.0 °C). It is well known that the P=O systems are generally 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 and favors O over S.³ The natural bond order (NBO) charges [B3LYP/6-311+G(d,p) level of theory]⁴ of the reaction center P in the gas phase are 1.793 (**1O**),^{1m} 1.180 (**1S**),^{1m} 1.844 (**2O**),^{1l} and 1.236 (**2S**),^{1d} which are consistent with the inductive effects of Ph ($\sigma_1 = +0.12$) and Me ($\sigma_1 = -0.01$) ligands.⁵ The NBO charges on the P atom of P=O systems are greater (*ca.* 0.6) than those of their P=S counterparts, implying the electronegativity difference between O and S.

Solely considering the positive charge of the reaction center

P atom (or the electronic influence of the two ligands), the pyridinolysis ($\text{C}_5\text{H}_5\text{N}$) rate of **1O** (and **1S**) should be slower than that of **2O** (and **2S**), i.e., $k_2(\mathbf{1O})/k_2(\mathbf{2O}) < 1$ [and $k_2(\mathbf{1S})/k_2(\mathbf{2S}) < 1$]. However, the observed rate ratio of $k_2(\mathbf{1O})/k_2(\mathbf{2O}) = 1,870$ is completely opposite to expectations from the inductive effects of the ligands. At a glance, the rate ratio of $k_2(\mathbf{1S})/k_2(\mathbf{2S}) = 0.41$ seems to be consistent with expectations from the inductive effects of the ligands. The sequence of $\sum\sigma_1$ of the two ligands is -0.02 (Me_2 : **1O** and **1S**) < 0.24 (Ph_2 : **2O** and **2S**) < 0.52 [$(\text{PhO})\text{Ph}$] < 0.56 [$(\text{EtO})_2$] < 0.60 [$(\text{MeO})_2$] < 0.80 [$(\text{PhO})_2$].⁵ However the sequence of the second-order rate constants of the pyridinolyses ($\text{C}_5\text{H}_5\text{N}$) of P=O and P=S systems in MeCN at 35.0 °C is as follows: $k_2 \times 10^3 \text{ M}^{-1} \text{ s}^{-1} = 102,000$ [**1O**: $\text{Me}_2\text{P}(=\text{O})\text{Cl}$] < 266 [$(\text{PhO})_2\text{P}(=\text{O})\text{Cl}$]^{1a} < 64.7 [$(\text{MeO})_2\text{P}(=\text{O})\text{Cl}$]^{1g} < 54.6 [**2O**: $\text{Ph}_2\text{P}(=\text{O})\text{Cl}$]^{1d} < 52.8 [$(\text{EtO})_2\text{P}(=\text{O})\text{Cl}$]^{1g} and 0.744 [**1S**: $\text{Me}_2\text{P}(=\text{S})\text{Cl}$] < 1.19 [$(\text{EtO})_2\text{P}(=\text{S})\text{Cl}$]^{1d} < 1.54 [$(\text{MeO})_2\text{P}(=\text{S})\text{Cl}$]^{1g} < 1.83 [**2S**: $\text{Ph}_2\text{P}(=\text{S})\text{Cl}$]^{1d} < 11.4 [$(\text{PhO})\text{PhP}(=\text{S})\text{Cl}$]^{1f}. There is no linear correlation between $\sum\sigma_1$ and k_2 for both P=O and P=S systems. Regarding to the anilinolysis ($\text{C}_6\text{H}_5\text{NH}_2$) in MeCN at 55.0 °C, the rate ratios of $k_2(\mathbf{1O})/k_2(\mathbf{2O}) = 4,520$ ^{1l,q} and $k_2(\mathbf{1S})/k_2(\mathbf{2S}) = 16$ ^{1m,r} were also contrary to expectations for the electronic influence of the two ligands. It should be noted that the electrophilicity of the substrate is the major factor to determine the reactivity of the phosphoryl transfer reaction as can be seen in “thio effect”, i.e., P=O system has a greater reactivity compared to its P=S counterpart. However, the electronic influence of the two ligands on the aminolysis rate is no more major factor within *each* reaction system, P=O or P=S.

The authors reported that the degree of steric hindrance of the two ligands is the major factor to determine the anilinolysis rates of both the P=O and P=S systems in MeCN.^{11t} However, the sequence of the pyridinolysis rates of both the P=O and

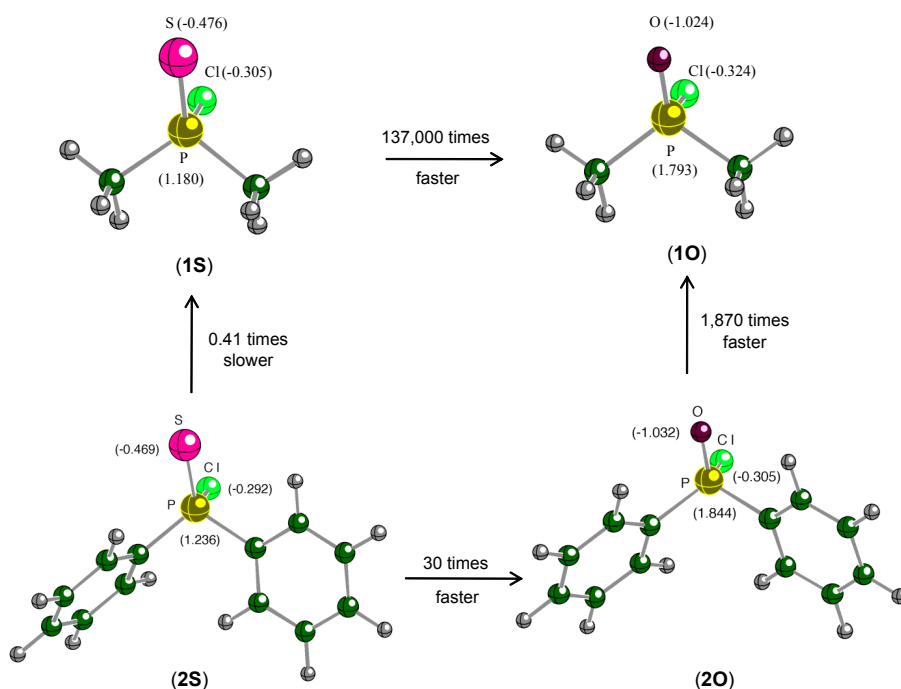
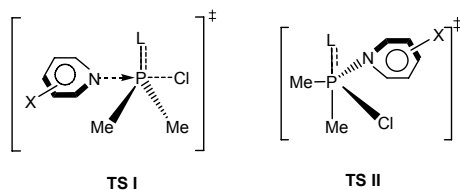


Figure 3. The B3LYP/6-311+G(d,p) geometries and NBO charges of **1O**, **1S**, **2O**,^{1d} and **2S**^{1d} in the gas phase. The pyridinolysis ($\text{C}_5\text{H}_5\text{N}$) rate ratios in acetonitrile at 35.0 °C are displayed next to the arrows.

P=S systems is not linearly correlated with the summations of steric parameters (E_s) of the two ligands; $\sum E_s = 0.00$ (Me₂: **10** and **1S**) < 4.43 [(MeO)₂] < 4.67 [(EtO)₂] < 4.96 (Ph₂: **20** and **2S**) < 5.11 [(PhO)Ph] < 5.35 [(PhO)₂].⁶ Thus, it is evident that neither the electronic influence nor the degree of steric hindrance of the two ligands is not the major factor to determine the pyridinolysis rates of both the P=O and P=S systems.

As seen in Figs. 1-2, the Hammett and Brønsted plots for substituent X variations for the pyridinolyses of **10** (with a break region between 3-phenyl and 3-MeO pyridines) and **1S** (with a break point at pyridine) exhibit biphasic concave upwards, as observed in the pyridinolyses of aryl phenyl isothiocyanophosphates [(YC₆H₄O)(PhO)P(=O)NCS],^{1c} **2S**,^{1d} dimethyl [(MeO)₂P(=S)Cl],^{1g} and diethyl [(EtO)₂P(=S)Cl]^{1g} chlorothionophosphates in MeCN. Biphasic concave upward Hammett plots for substituent Z (substituent in the leaving group) variations were also observed for the pyridinolyses of Z-N-aryl-P,P-diphenyl phosphinic amides [Ph₂P(=O)NHPH₂] in DMSO.^{1h} Herein, the magnitudes of ρ_X and β_X of strongly basic pyridines are greater than those of weakly basic pyridines, and those of **1S** are greater than those of **10**.

The authors propose concerted mechanism for the pyridinolyses of both **10** and **1S** on the basis of the same reason as discussed earlier for the pyridinolyses of aryl phenyl isothiocyanophosphates,^{1c} diphenyl thiophosphinic chloride,^{1d} dimethyl,^{1g} and diethyl^{1g} chlorothionophosphates. Biphasic concave upward free energy relationships for substituent X variations were rationalized by a change of nucleophilic attacking direction from a dominant backside [apical position in the trigonal bipyramidal pentacoordinate (TBP-5C) transition state (TS) I] towards the Cl leaving group for weakly basic pyridines to a dominant frontside (equatorial position in the TBP-5C TS II) for strongly basic pyridines, in which the pyridine and Cl occupy adjacent spaces in the TS.^{1c,d,g}



The unusual positive ρ_X ($=+0.16$) and negative β_X ($=-0.03$) values of **10** (Table 1 and Fig. 1) for the weakly basic pyridines (X = 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, and 4-CN) can be occurred because of (i) desolvation of ground state, (ii) TS imbalance, or (iii) isokinetic relationship.

(i) The discrete linear free energy relationships are reported because of a desolvation step prior to the rate-limiting nucleophilic attack with a smaller value of β_X when the nucleophile is anion and the solvent is polar protic, e.g., water.⁷ However, in the present work, the positive ρ_X (and negative β_X) value for the less basic pyridines are not ascribed to a desolvation step prior to the rate-limiting nucleophilic attack, since the pyridine nucleophile is neutral and the MeCN solvent is dipolar aprotic.

(ii) The authors reported that the sign of ρ_X changes from positive for the relatively strong electron-donating Y substituents to negative for the more electron-withdrawing substituents

of the reactions of 1-(Y-phenyl) ethyl chlorides with X-anilines in methanol.⁸ The anilinolyses of Y-benzhydryl chlorides in MeOH-MeCN also exhibited the change of the sign of ρ_X depending on Y substituents.⁹ The positive ρ_X values were interpreted in terms of a TS structure in which nearly complete bond formation between the nucleophile and cation formed in an ion-pair pre-equilibrium is coupled with a TS imbalance phenomenon, advocated by Jencks¹⁰ and Bernasconi.¹¹ However, the positive ρ_X value of **10** is inadequate to a TS imbalance phenomenon, since it only occurs in electron-withdrawing X substituents and P=O system.

(iii) For a large number of reaction series, it is found that $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ are proportional.¹² The observed second-order rate constants of **10** with 3-methoxy, 4-acetyl, and 4-cyano pyridines are 1.30, 1.01, $0.835 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ at -20.0°C and 2.26, 1.56, $1.43 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ at -15.0°C , respectively. It should be noted that the sequence of the pyridinolysis rate is changed from 3-MeO < 4-Ac < 4-CN with $\rho_X = +0.16$ at -25.0°C via 3-MeO > 4-Ac > 4-CN with $\rho_X = -0.34$ at -20.0°C to 3-MeO > 4-Ac > 4-CN with $\rho_X = -0.38$ at -15.0°C as shown in Fig. 4. The isokinetic temperature according to eq 3 is $T_{\text{ISOKINETIC}} = 249.4^\circ \text{K} = -23.8^\circ \text{C}$ (Fig. 5), based on $\Delta H^\ddagger = 26.2$ and $\Delta S^\ddagger = -54$ for X =

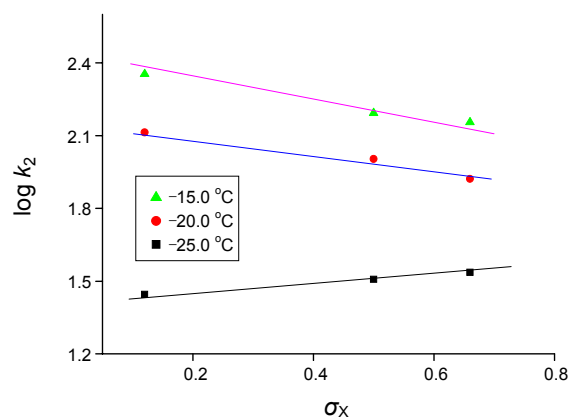


Figure 4. The Hammett ($\log k_2$ vs σ_X) plots of the reactions of **10** [Me₂P(=O)Cl] with 3-MeO, 4-Ac, and 4-CN pyridines in MeCN at -15.0 , -20.0 , and -25.0°C . The ρ_X values are -0.38 at -15.0 , -0.34 at -20.0 , and $+0.16$ at -25.0°C .

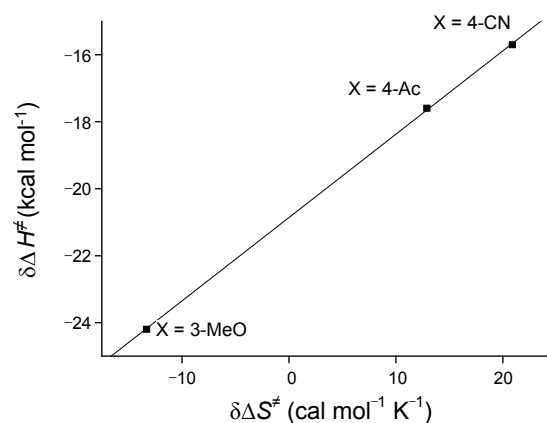


Figure 5. Isokinetic relationship of the reactions of **10** [Me₂P(=O)Cl] with 3-MeO, 4-Ac, and 4-CN pyridines in MeCN resulting in isokinetic temperature (slope), $T_{\text{ISOKINETIC}} = 249.4^\circ \text{K} = -23.8^\circ \text{C}$.

3-MeO; $\Delta H^\ddagger = 19.6$ and $\Delta S^\ddagger = -28$ for X = 4-Ac; $\Delta H^\ddagger = 17.7$ kcal/mole and $\Delta S^\ddagger = -20$ eu for X = 4-CN.

$$\delta\Delta G^\ddagger = \delta\Delta H^\ddagger - T\delta\Delta S^\ddagger = 0 \text{ when } \delta\Delta H^\ddagger = T_{\text{ISOKINETIC}} \delta\Delta S^\ddagger \quad (3)$$

In summary, the pyridinolyses of dimethyl phosphinic (**10**) and thiophosphinic chlorides (**1S**) are studied kinetically in MeCN at -25.0 and 35.0 °C, respectively. Both reactions proceed through concerted mechanism, and exhibit biphasic concave upward free energy relationships due to a change of nucleophilic attacking direction. The unusual positive ρ_X and negative β_X values of **10** for the weakly basic pyridines are ascribed to isokinetic relationship.

Experimental Section

Materials. GR grade dimethyl phosphinic (**10**) (min 97%) and thiophosphinic (**1S**) chlorides (min. 98%), were 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 measurements. 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-h} using large excesses of nucleophiles, $[\mathbf{10}] = 0.001$ M and $[\text{XC}_5\text{H}_4\text{N}] = 0.01 - 0.022$ M; $[\mathbf{1S}] = 0.001$ M and $[\text{XC}_5\text{H}_4\text{N}] = 0.01 - 0.05$ M. Each pseudo-first-order rate constants value (k_{obsd}) was averaged obtained from more than three runs, which were reproducible within $\pm 3\%$.

Product analysis. Dimethyl phosphinic (at -25.0 °C) and thiophosphinic (at 35.0 °C) chlorides were reacted with excess pyridine for more than 15 half-lives in acetonitrile, as previously described.^{1fg} 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:

(CH₃)₂P(=O)N⁺C₅H₅Cl⁻: Dark yellow liquid; ¹H NMR (400 MHz, CDCl₃) δ 1.44, 1.45, 1.46, 1.47, 1.48, 1.49, 1.51, 1.52 (6H, m, CH₃), 7.21, 7.23, 7.24, 7.95, 7.96, 7.97, 8.41, 8.41, 8.42, 8.43, 8.89 (5H, m, pyridine); ¹³C NMR (100 MHz, CDCl₃) δ 16.16 (CH₃), 17.12 (CH₃), 127.04, 141.41, 145.352, 149.09 (C=C, pyridine); ³¹P NMR (162 MHz, CDCl₃) δ 59.33 (1P, s, P=O); m/z , 156 (M⁺); Anal. Calcd for C₇H₁₁ClNOP: C, 43.9; H, 5.8; N, 7.3. Found: C, 44.2; H, 5.7; N, 7.4.

(CH₃)₂P(=S)N⁺C₅H₅Cl⁻: White solid; mp 98 - 100 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.05, 2.06, 2.07, 2.08, 2.09 (6H, m, CH₃), 7.98, 8.00, 8.02, 8.05, 8.88, 8.89 (5H, m, pyridine); ¹³C NMR (100 MHz, CDCl₃) δ 25.75, (CH₃), 26.48 (CH₃), 127.10, 141.05, 145.57 (C=C, pyridine); ³¹P NMR (162 MHz, CDCl₃) δ 98.59 (1P, s, P=S); m/z , 172 (M⁺) (HRMS).

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