

Pyridinolysis of Bis(*N,N*-dimethylamino) Phosphinic Chloride in Acetonitrile

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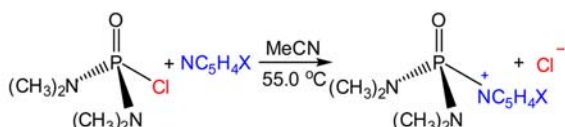
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Received October 27, 2011, Accepted November 7, 2011**Key Words** : Phosphoryl transfer reaction, Pyridinolysis, Bis(*N,N*-dimethylamino) phosphinic chloride, Biphasic concave upward free energy relationship

The kinetic studies of the pyridinolyses of tetracoordinated phosphorus have been studied extensively by this lab.¹ In the present work, the nucleophilic substitution reactions of bis(*N,N*-dimethylamino) phosphinic chloride (**3**) with substituted X-pyridines are investigated kinetically in acetonitrile (MeCN) at 55.0 ± 0.1 °C (Scheme 1) to gain further systematic information into the reactivity and mechanism depending on the variation of the two ligands, as well as to compare with the relevant phosphinic chloride systems: dimethyl [**1**: $\text{Me}_2\text{P}(=\text{O})\text{Cl}$],^{1h} diethyl [**2**: $\text{Et}_2\text{P}(=\text{O})\text{Cl}$],¹ⁱ dicyclohexyl [**4**: $\text{cHex}_2\text{P}(=\text{O})\text{Cl}$],¹ⁿ methyl phenyl [**5**: $\text{MePhP}(=\text{O})\text{Cl}$],^{1m} and diphenyl [**6**: $\text{Ph}_2\text{P}(=\text{O})\text{Cl}$]^{1d} phosphinic chlorides on the basis of the magnitude of positive charge of the reaction center P atom, steric effects of the two ligands, and selectivity parameters. The numbering of the substrates follows the sequence of the summations of the Taft's steric constants [$\Sigma E_s = E_s(\text{R}_1) + E_s(\text{R}_2)$] of the two ligands.²

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

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



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 reactions of bis(*N,N*-dimethylamino) phosphinic chloride (**3**) with X-pyridines in MeCN at 55.0 °C.

The second-order rate constants [k_2 ($\text{M}^{-1} \text{s}^{-1}$)] are summarized in Table 1. The Brønsted β_X value was calculated by correlating $\log k_2(\text{MeCN})$ with $\text{p}K_a(\text{H}_2\text{O})$,³ which was justified theoretically and experimentally.⁴ The substituent effects of the nucleophiles upon the pyridinolysis rates are compatible with a typical nucleophilic substitution reaction where the stronger nucleophile leads to a faster rate. However, both the Hammett ($\log k_2$ vs σ_X ; Fig. 1) and Brønsted [$\log k_2$ vs $\text{p}K_a(\text{X})$; Fig. 2] plots are biphasic concave upwards with a break point at X = H. The magnitudes of ρ_X ($= -4.36$) and β_X ($= 0.94$) values with the strongly basic pyridines (X = 4-MeO, 4-Me, 3-Me, H) are considerably greater than those ($\rho_X = -1.98$ and $\beta_X = 0.33$) with the weakly basic pyridines (X = H, 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

The second-order rate constants (k_2) with unsubstituted pyridine ($\text{C}_5\text{H}_5\text{N}$) at 35.0 °C, natural bond order (NBO) charges at the reaction center P atom in the gas phase

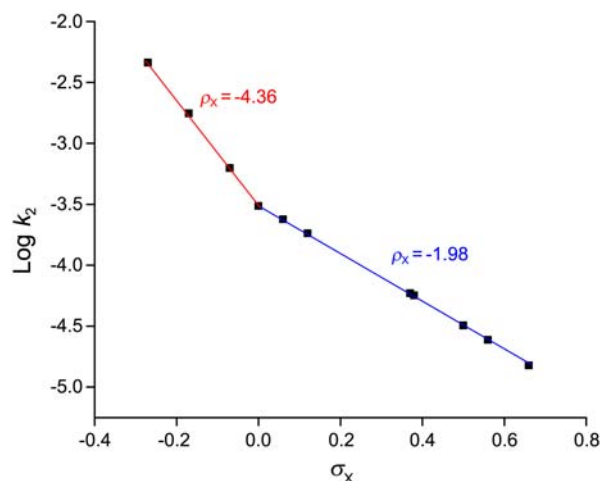


Figure 1. The Hammett plot ($\log k_2$ vs σ_X) of the reactions of bis(*N,N*-dimethylamino) phosphinic chloride (**3**) with X-pyridines in MeCN at 55.0 °C. The values of ρ_X are -4.36 ± 0.01 ($r = 0.999$) with X = (4-MeO, 4-Me, 3-Me, H) and -1.98 ± 0.01 ($r = 0.999$) with X = (H, 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN).

Table 1. Second-Order Rate Constants ($k_2 \times 10^4/\text{M}^{-1} \text{s}^{-1}$) of the Reactions of Bis(*N,N*-dimethylamino) Phosphinic Chloride (**3**) with $\text{XC}_5\text{H}_4\text{N}$ in MeCN at 55.0 °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	45.9	17.6	6.26	3.07	2.38	1.83	0.589	0.566	0.321	0.244	0.150
$\times 10^4$	± 0.1	± 0.1	± 0.03	± 0.02	± 0.02	± 0.01	± 0.003	± 0.005	± 0.001	± 0.002	± 0.001

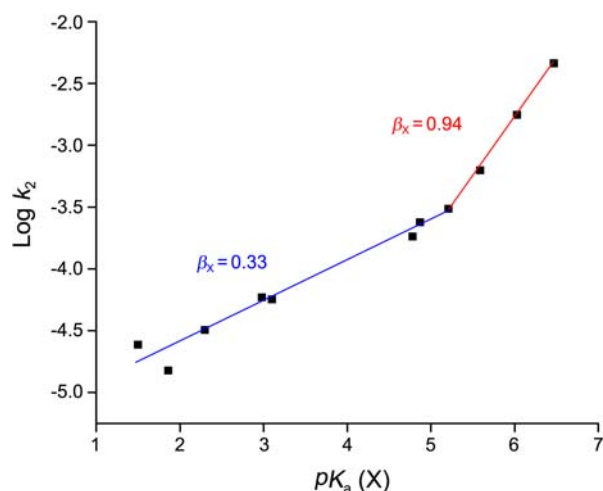


Figure 2. The Brønsted plot [$\log k_2$ vs $pK_a(X)$] of the reactions of bis(*N,N*-dimethylamino) phosphinic chloride (**3**) with *X*-pyridines in MeCN at 55.0 °C. The values of β_X are 0.94 ± 0.03 ($r = 0.999$) with $X = (4\text{-MeO}, 4\text{-Me}, 3\text{-Me}, \text{H})$ and 0.33 ± 0.10 ($r = 0.981$) with $X = (\text{H}, 3\text{-Ph}, 3\text{-MeO}, 3\text{-Cl}, 3\text{-Ac}, 4\text{-Ac}, 3\text{-CN}, 4\text{-CN})$.

[B3LYP/6-311+G(d,p) level of theory],⁵ summations of the Taft's steric constants [$\Sigma E_s = E_s(R_1) + E_s(R_2)$] of the two ligands,² Brønsted coefficients (β_X), and variation trends of the free energy relationships with *X* for the pyridinolyses of six phosphinic chloride system in MeCN are summarized in Table 2. When the magnitude of the positive charge of the reaction center P atom in the substrate plays an important role to determine the pyridinolysis rate, the sequence of the pyridinolysis rate should be $3 > 4 > 6 > 5 > 2 > 1$. On the other hand, when the steric effects of the two ligands, R_1 and R_2 , play an important role, the sequence of the rate should be $1 > 2 > 3 > 4 > 5 > 6$. The pyridinolysis rate is very sensitive to the two ligands, however, the observed sequence of $5 > 1 \gg 2 > 6 \gg 3 > 4$, giving the relative rate ratio of $7.6 \times 10^6(5):6.1 \times 10^6(1):7.7 \times 10^3(2):3.3 \times 10^3(6):10(3):1(4)$, does not show systematic consistency with the NBO charge at P atom or ΣE_s of the two ligands. These results indicate that the pyridinolysis rates of phosphinic chloride system in MeCN are not dependent upon one dominant factor but on many factors. In contrast, the anilinolysis rates of the phosphinic chloride systems⁷ are predominantly dependent

upon the steric effects of the two ligands when excluding **3**^{7a} and **4**,^{7b} and the sequence of the anilinolysis rate is $1 > 2 > 5 > 6$, giving the relative rate ratio of $4.5 \times 10^3(1)^{7c}:1.1 \times 10^2(2)^{7d}:80(5)^{7c}:1(6)^{7e}$ in MeCN at 55.0 °C. Herein, both the pyridinolysis and anilinolysis rates of **3** and **4** show exceptionally slow rate to be rationalized by the conventional stereoelectronic effects, and further studies are required to clarify the considerably low reactivity.

The variation trends of the free energy relationships with *X* for the pyridinolyses of six (**1-6**) substrates are not same but dependent upon the two ligands: (i) in **1**, biphasic concave upwards with a break region between $X = 3\text{-Ph}$ and 3-MeO , giving unusual positive ρ_X (and negative β_X) value with the weakly basic pyridines at 25.0 °C; (ii) in **2** and **6**, linear; (iii) in **3**, biphasic concave upwards with a break point at $X = \text{H}$; (iv) in **4**, biphasic concave upwards with a break point at $X = 3\text{-Ph}$; (v) in **5**, biphasic concave downwards with a break point at $X = \text{H}$, giving unusual positive ρ_X (and negative β_X) value with the strongly basic pyridines at 20.0 °C.

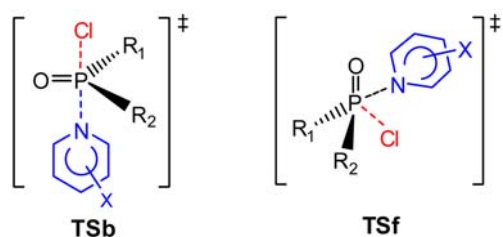
The isokinetic relationships for the pyridinolyses of tetra-coordinated phosphorus are observed when the reaction temperatures are considerably low: (i) the pyridinolysis of **1** yielded isokinetic temperature, $T_{\text{ISOKINETIC}} = 249.4 \text{ K} = -23.8$ °C, with the weakly basic pyridines;^{1h} (ii) the pyridinolysis of **5** at -20.0 °C yielded $T_{\text{ISOKINETIC}} = 287.5 \text{ K} = 14.4$ °C with the strongly basic pyridines, indicating that the free energy relationships, i.e., the Hammett and Brønsted plots, change from concave downwards below 14.4 °C to concave upwards above 14.4 °C;^{1m} (iii) the pyridinolysis of ethylene phosphorochloridate [$\text{C}_2\text{H}_4\text{OOP(=O)Cl}$] yielded biphasic concave upward free energy correlation with a break point at $X = 3\text{-Ph}$, giving unusual positive ρ_X (and negative β_X) value with the weakly basic pyridines in MeCN at -20.0 °C, and exhibited $T_{\text{ISOKINETIC}} = 279.7 \text{ K} = 6.6$ °C.^{1u} It seems that the pyridinolysis of tetra-coordinated phosphorus shows the isokinetic relationship in MeCN when the free energy correlation exhibits biphasic concave upwards (or downwards) with min (or max) rate constant at the very low temperature.

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

Table 2. Summary of the Second-Order Rate Constants (k_2) with $\text{C}_5\text{H}_5\text{N}$ at 35.0 °C, NBO Charges at the Reaction Center P Atom, Summations of the Taft's Steric Constants (ΣE_s) of the Two Ligands, Brønsted Coefficients (β_X), and Variation Trends of Free Energy Relationships with *X* for the Reactions of Phosphinic Chlorides (**1-6**) with $\text{XC}_5\text{H}_4\text{N}$ in MeCN

Substrate	$k_2 \times 10^{3a}$	Charge at P	$-\Sigma E_s$	β_X	Trend ^k	Ref.
1: O(Me,Me)	102,000 ^b	1.793	0	0.17/−0.03 ^{e,f}	V	1h
2: O(Et,Et)	127	1.817	0.14	0.45 ^g	L	1i
3: O(NMe ₂ ,NMe ₂)	0.173 ^c	2.165	0.94 ^d	0.94/0.33 ^{e,h}	V	this work
4: O(cHex,cHex)	0.0166	1.863	1.58	1.23/0.14 ^{e,h}	V	1n
5: O(Me,Ph)	126,000 ^b	1.821	2.48	−0.48/1.17 ^{e,i}	Λ	1m
6: O(Ph,Ph)	54.6	1.844	4.96	0.68 ^j	L	1d

^aSecond-order rate constant with unsubstituted pyridine ($X = \text{H}$) at 35.0 °C. ^bExtrapolated value in the Arrhenius plot. See refs. 1h and 1m. ^cExperimental kinetic data. See ref. 6. ^dThe value of $E_s = 0.47$ with *i*-Pr is introduced because of the lack of data with NMe₂. ^eStrongly/weakly basic pyridines. ^fThe values at -25 °C. ^gThe value at 45 °C. ^hThe values at 55 °C. ⁱThe values at -20 °C. ^jThe value at 35 °C. ^kV, L, and Λ indicate that the free energy relationships are concave upwards, linear, and concave downwards with *X*, respectively.



Scheme 2. Backside attack TSb and frontside attack TSf.

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.⁸ These statements cannot be an iron rule. 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.¹⁸ Furthermore, the change from concave downward below 14.4 °C to concave upward free energy relationship above 14.4 °C of the pyridinolysis of **5** cannot be substantiated by the different mechanism between below 14.4 °C as a mechanism change and above 14.4 °C as a rate-limiting step change, i.e., the reaction mechanism is the same either below 14.4 °C or above 14.4 °C. 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 TSb (Scheme 2).^{1c}

When the free energy relationships are not linear with X, the β_X values with the strongly basic pyridines are greater than those with the weakly basic pyridines for the pyridinolyses of **1**, **3**, and **4**, whereas the β_X value with the strongly basic pyridines is smaller than that with the weakly basic pyridines for the pyridinolysis of **5**. The β_X values of **2** and **4** are somewhat greater than those of **1**, **3**, and **4** with the weakly basic pyridines. In the pyridinolyses of **1** and **4**, a concerted mechanism was proposed, and biphasic concave upward free energy relationships was interpreted as a change of nucleophilic attacking direction from a frontside attack (TSf) with the strongly basic pyridines to a backside attack (TSb) with the weakly basic pyridines. The S_N2 reaction mechanism was proposed for the pyridinolyses of **2** and **6** with both frontside (TSf) and backside attacks (TSb), 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 (0.45 with **2** and 0.68 with **6**) values.^{1d,l} In the pyridinolyses of **5**,^{1h} a stepwise mechanism with a rate-limiting step change from bond breaking with the weakly basic pyridines to bond formation with the strongly basic pyridines was proposed on the basis of the magnitudes of β_X values. In the present work of **3**, a concerted mechanism is proposed, and biphasic concave upward free energy relationships is interpreted as a change of nucleophilic attacking direction from a dominant frontside attack (TSf; $\beta_X = 0.94$) with the strongly basic pyridines to a dominant backside attack (TSb; $\beta_X = 0.33$) with the weakly basic pyridines.

In summary, the kinetic studies on the pyridinolysis of bis(*N,N*-dimethylamino) phosphinic chloride have been carried out in acetonitrile at 55.0 °C. The free energy correlations for substituent X variations in the X-pyridines are biphasic concave upwards with a break point at X = H. A concerted S_N2 mechanism is proposed with a change of the attacking direction of the X-pyridine from a frontside attack with the strongly basic pyridines to a backside attack with the weakly basic pyridines on the basis of greater β_X value with more basic pyridines than with less basic pyridines.

Experimental Section

Materials. Bis(*N,N*-dimethylamino) phosphinic chloride, commercially available, was used without further purification. GR grade pyridines and HPLC grade MeCN (less than 0.005% water content) were used without further purification.

Kinetic Procedure. Conductometric rate measurements were carried out using self-made computer-aided automatic A/D converter conductivity bridges.^{1,7} Pseudo-first-order rate constants, k_{obsd} , were measured by curve fitting analysis in origin program with a large excess of pyridines, [Substrate] = 5×10^{-4} M and [Pyridine] = (0.1-0.3) M. Second-order rate constants, k_2 , were obtained from the slope of a plot of k_{obsd} vs [X-Pyridine]. The Pseudo-first-order rate constant values (k_{obsd}) were the average of at least three runs that were reproducible within $\pm 3\%$.

Product Analysis. Bis(*N,N*-dimethylamino) phosphinic chloride was reacted with excess pyridine for more than 15 half-lives in MeCN at 55.0 °C. Solvent was removed under reduced pressure. The product was isolated after treatment with ether and MeCN, and then dried under reduced pressure. The analytical and spectroscopic data of the product are summarized as follows:

$[\text{N}(\text{CH}_3)_2]_2\text{P}(=\text{O})\text{NC}_5\text{H}_5]^+\text{Cl}^-$. White solid crystal; mp 141-142 °C; ¹H-NMR (400 MHz, CDCl₃ & TMS) δ 2.65-2.76 (aliphatic, 12H, m), 7.72-9.51 (aromatic, 5H, m); ¹³C-NMR (100 MHz, CDCl₃ & TMS) δ 34.73 (aliphatic, 4C, s), 126.01-144.09 (aromatic, 5C, s); ³¹P-NMR (162 MHz, CDCl₃ & TMS) δ 15.12 (1P, s, P=O); GC-MS for C₉H₁₇N₃OP⁺ (EI, *m/z*), 214 (M⁺).

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