Pyridinolysis of Aryl *N,N*-Dimethyl Phosphoroamidochloridates

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The kinetic studies on the reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates (**1**) with X-anilines and deuterated anilines in acetonitrile (MeCN) were reported by this lab.[1] Herein, the free energy relationships with both X and Y were all linear, and the secondary inverse deuterium kinetic isotope effects ($k_H/k_D < 1.0$) were rationalized by a dominant backside nucleophilic attack, and a stepwise mechanism with a rate-limiting leaving group departure from the intermediate was proposed based on the positive ρ_{XY} value. In the present work, the nucleophilic substitution

X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-Ac, 4-Ac
Y = 4-MeO, 4-Me, H, 3-MeO, 4-Cl

Scheme 1. Pyridinolysis of Y-aryl *N,N*-dimethyl phosphoroamidochloridates (**1**) in MeCN at 35.0 ºC.

reactions of **1** with X-pyridines have been studied kinetically in MeCN at 35.0 ± 0.1 ºC (Scheme 1) to gain further information on the phosphoryl transfer reactions and substituent effects of the nucleophiles and substrates on the reaction mechanism.

Results and Discussion

Tables 1-3 list the second-order rate constants, ρ_X and β_X with X, and ρ_Y with Y, respectively. The effects of substituents X and Y in the incoming pyridine and leaving group on reactivity, respectively, are in line with those for a typical nucleophilic substitution reaction. The Brönsted [Fig. 1; log k_2 *vs* pK_a(X)] and Hammett (Fig. S1; log k_2 *vs* σ_X) plots for substituent X variations in the nucleophiles, however, exhibit biphasic concave upwards with a break point at X = 3-Ph, while the Hammett plots (Fig. S2; log k_2 *vs* σ_Y) for substituent Y variations in the substrates exhibit linear. The magnitudes of the β_X and ρ_X values with *a*-block

Table 1. Second-Order Rate Constants ($k_2 \times 10^4$/M^{-1} s^{-1}) of Reactions of **1** with X-Pyridines in MeCN at 35.0 ºC

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	158 ± 1	192 ± 1	222 ± 1	275 ± 1	471 ± 1
4-Me	50.9 ± 0.1	60.9 ± 0.1	70.9 ± 0.1	80.8 ± 0.1	118 ± 1
3-Me	15.2 ± 0.1	17.5 ± 0.1	21.1 ± 0.1	23.2 ± 0.1	32.6 ± 0.1
H	5.86 ± 0.01	7.05 ± 0.01	8.46 ± 0.01	9.38 ± 0.01	12.1 ± 0.1
3-Ph	2.56 ± 0.01	2.87 ± 0.02	3.18 ± 0.01	3.66 ± 0.01	4.13 ± 0.02
3-Ac	1.12 ± 0.01	1.24 ± 0.02	1.35 ± 0.02	1.55 ± 0.01	1.73 ± 0.01
4-Ac	0.849 ± 0.001	0.927 ± 0.001	0.998 ± 0.001	1.16 ± 0.01	1.26 ± 0.01

Table 2. Hammett (ρ_X)[a] and Brönsted (β_X)[b] Coefficients with X of Reactions of **1** with X-Pyridines in MeCN at 35.0 ºC

X \ Y		4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO~3-Ph	$-\rho_X$	5.42 ± 0.03	5.50 ± 0.04	5.53 ± 0.06	5.62 ± 0.04	6.12 ± 0.05
(*a*-block)	β_X	1.12 ± 0.02	1.14 ± 0.02	1.15 ± 0.02	1.17 ± 0.02	1.27 ± 0.03
3-Ph~4-Ac	$-\rho_X$	1.10 ± 0.01	1.12 ± 0.01	1.13 ± 0.01	1.14 ± 0.01	1.17 ± 0.01
(*b*-block)	β_X	0.19 ± 0.03	0.20 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.21 ± 0.01

[a]Correlation coefficients (r) are better than 0.998. [b]r = 0.999

Table 3. Hammett Coefficients (ρ_Y)[a] with Y of Reactions of **1** with X-Pyridines in MeCN at 35.0 ºC

| X	4-MeO	4-Me	3-Me	H	3-Ph	3-Ac	4-Ac
ρ_Y	0.84 ± 0.07	0.65 ± 0.04	0.60 ± 0.03	0.58 ± 0.02	0.40 ± 0.01	0.37 ± 0.01	0.34 ± 0.01

[a]r = 0.945-0.991
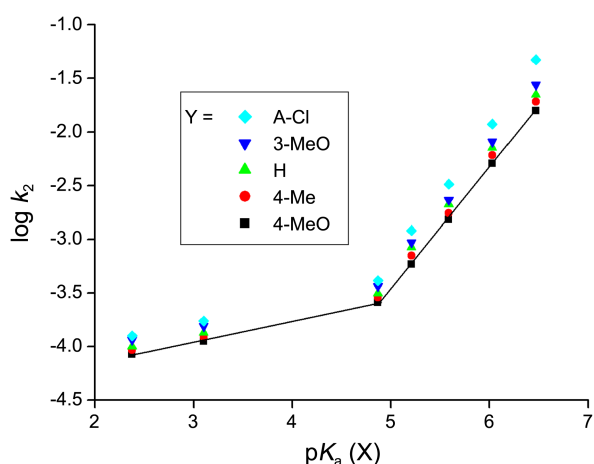
Figure 1. Brönsted plots with X of reactions of **1** with X-pyridines in MeCN at 35.0 °C.

(X = 4-MeO, 4-Me, 3-Me, H, 3-Ph) are 5-6 times greater than those with *b*-block (X = 3-Ph, 3-Ac, 4-Ac), suggesting greater degree of bond formation with *a*-block than with *b*-block. The ρ_X values consistently decrease (or more negative value; $\partial\rho_X < 0$) as the substituent Y becomes more electron-withdrawing ($\partial\sigma_Y > 0$), giving $\partial\rho_X/\partial\sigma_Y = (-)/(+) < 0$ for both *a*- and *b*-block, while the ρ_Y values invariably decrease (or less positive value; $\partial\rho_Y < 0$) as the pyridine becomes less basic ($\partial\sigma_X > 0$), giving $\partial\rho_Y/\partial\sigma_X = (-)/(+) < 0$ for both *a*- and *b*-block.

The pyridinolysis rate is faster than the anilinolysis rate, *e.g.*, $k_{Pyr}/k_{An} = (16.8 \times 10^{-4})/(1.10 \times 10^{-4}) = 15.3$ when X = Y = H in MeCN at 55.0 °C.[2] This is in accord with the basicity (or nucleophilicity) of the nucleophiles: $pK_a(Pyr) = 12.33$ and $pK_a(An) = 10.56$ in MeCN;[3] $pK_a(Pyr) = 5.17$ and $pK_a(An) = 4.58$ in water.[4]

Figure 2 shows the two ρ_{XY} values with *a*- and *b*-block, respectively, because the Hammett plots with X are biphasic. The cross-interaction constants (CICs; ρ_{XY}) are obtained according to the definition: $\log (k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y$ and $\rho_{XY} = \partial^2\log (k_{XY}/k_{HH})/\partial\sigma_X\partial\sigma_Y = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X$.[5] The sign of ρ_{XY} is negative for both *a*- ($\rho_{XY} = -1.15$) and *b*-block ($\rho_{XY} = -0.13$).[6] A concerted mechanism is proposed for both *a*- and *b*-block despite the biphasic concave upward free energy correlations for substituent X variations, because ρ_{XY} has a negative value in a concerted S$_N$2 (or a stepwise mechanism with a rate-limiting bond formation) while a positive value in a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate.[5] The anilinolysis of **1** proceeds via a stepwise process with a rate-limiting leaving group departure from the intermediate,[1] whereas the pyridinolysis of **1** proceeds via S$_N$2. This is not consistent with the general suggestion in which the concerted path becomes more likely to be followed with the weaker nucleophile while a stepwise path is favored with the stronger nucleophile.[7,8]

Bipasic concave upward free energy correlations with X can be substantiated by a change in the nucleophilic attacking direction towards the chlorde leaving group. A weakly
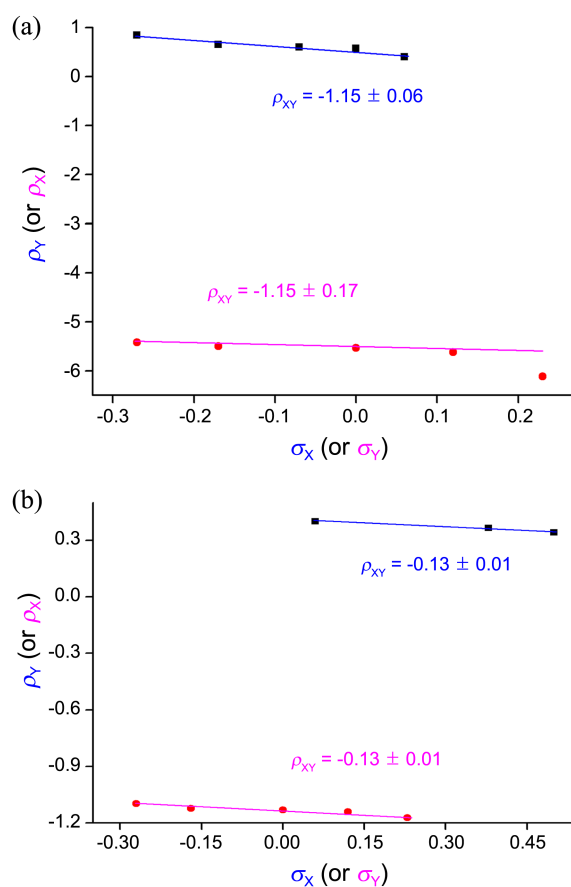
Figure 2. Plots of ρ_Y *vs* σ_X and ρ_X *vs* σ_Y of the reactions of **1** with X-pyridines in MeCN at 35.0 °C. The obtained ρ_{XY} values by multiple regression are: (a) $\rho_{XY} = -1.15 \pm 0.05$ (r = 0.996) with *a*-block; (b) $\rho_{XY} = -0.13 \pm 0.01$ (r = 0.998) with *b*-block.

basic group has a greater apicophilicity so that apical approach is favored for such nucleophiles.[8] 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 (= 1.12-1.27) values with *a*-block involving equatorial nucleophilic attack (*e.g.*, frontside attack TSf in Scheme 2) are obtained compared to those ($\beta_X = 0.19$-0.21) with *b*-block involving apical nucleophilic attack (*e.g.*, backside attack TSb in Scheme 2). The magnitudes of the ρ_{XY} (= −1.15 and −0.13 with *a*- and *b*-block, respectively) values are consistent with the β_X (= 0.12-1.27 and 0.19-0.21 with *a*- and *b*-block, respectively) values because the magnitude of the ρ_{XY} value is inversely proportional to the distance between X and Y
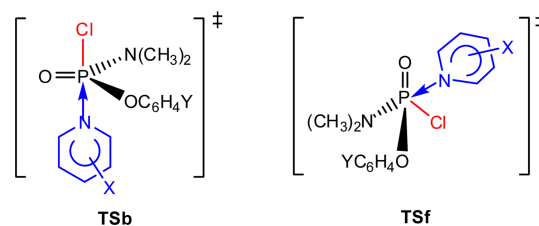
Scheme 2. Backside apical attack TSb with *b*-block and frontside equatorial attack TSf with *a*-block.

through the reaction center.[5]

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.[9] It is the suggestion of the authors that the biphasic concave upward free energy correlation is also diagnostic of a change in the direction of the nucleophilic attack towards the leaving group from frontside equatorial with the strongly basic nucleophiles (*a*-block) to backside apical with the weakly basic nucleophiles (*b*-block).[10]

Table 4 lists the activation parameters, enthalpies and entropies of activation. The enthalpies of activation are relatively low (*ca.* 6 kcal mol^{-1}) and entropies of activation are relatively large negative value (*ca.* −50 cal mol^{-1} K^{-1}). There is no activation enthalpy-entropy compensation phenomena depending on the substituent Y in the substrates.[11] The relatively low value of activation enthalpy and large negative value of activation entropy are typical for the aminolyses of P=O (and P=S) systems regardless of the mechanism, either concerted (or stepwise with a rate-limiting bond formation) or stepwise with a rate-limiting bond cleavage.[12]

In summary, the nucleophilic substitution reactions of Y-aryl *N,N*-dimethyl phosphoroamidochlorides with X-pyridines are studied kinetically in acetonitrile at 35.0 ºC. The free energy correlations for substituent X variations in the nucleophiles exhibit biphasic concave upwards with a break point at X = 3-Ph. The negative sign of ρ_{XY} suggests that the reaction proceeds through a concerted mechanism for both *a*- (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph) and *b*-block (X = 3-Ph, 3-Ac, 4-Ac). The biphasic concave upward free energy relationships with X are rationalized by a change in the

nucleophilic attacking direction from frontside with *a*-block to backside with *b*-block.

Experimental Section

Materials. The substrates of Y-aryl *N,N*-dimethyl phosphoroamidochlorides were prepared as described previously.[1]

Kinetic Procedure. The second-order rate constants and selectivity parameters were obtained as reported earlier.[12b] The initial concentrations are as follows: [substrate] = 5 × 10^{-3} M and [XC$_5$H$_4$N] = (0.10-0.30) M.

Product Analysis. Phenyl *N,N*-dimethyl phosphoroamidochloridate was reacted with excess pyridine, for more than 15 half-lives at 35.0 ºC 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 and MeCN. Analytical and spectroscopic data of the product gave the following results (supporting information):

[(Me$_2$N)(PhO)P(=O)NC$_5$H$_5$]$^+$Cl$^-$. White gummy solid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 2.47-2.72 (d, 6H), 6.98-7.00 (t, 1H), 7.16-7.21 (d, 3H), 7.35-7.37 (t, 1H), 7.84-7.88 (t, 2H), 8.35-8.38 (t, 1H), 8.67-8.69 (d, 2H); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 35.0, 36.9, 121.2, 121.6, 124.8, 126.4, 127.9, 130.5, 131.0, 143.0, 143.1, 146.1, 153.6; ^{31}P-NMR (162 MHz, MeCN-d_3) δ −5.55 (1P, s, P=O); LC-MS for C$_{13}$H$_{16}$ClN$_2$O$_2$P (EI, *m/z*), 298 (M$^+$).

References and Notes

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6. The twenty five k_2 values (five nucleophiles × five substrates) are employed to calculate the ρ_{XY} value with *a*-block while fifteen k_2 values (three nucleophiles × five substrates) with *b*-block. The correlation coefficients with both blocks are acceptable.
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Table 4. Activation parameters for the reactions of **1** with C$_5$H$_5$N in MeCN

Y	t/ºC	$k_2 \times 10^4$ /M^{-1} s^{-1}	$\Delta H^{\ddagger}$ /kcal mol^{-1}	$-\Delta S^{\ddagger}$ /cal mol^{-1} K^{-1}
4-MeO	35.0	5.86 ± 0.01	6.4 ± 0.1	53 ± 1
	45.0	8.48 ± 0.01		
	55.0	11.8 ± 0.1		
4-Me	35.0	7.05 ± 0.01	6.2 ± 0.1	53 ± 1
	45.0	9.93 ± 0.01		
	55.0	13.9 ± 0.1		
H	35.0	8.46 ± 0.01	6.2 ± 0.2	53 ± 1
	45.0	11.8 ± 0.1		
	55.0	16.8 ± 0.1		
3-MeO	35.0	9.38 ± 0.01	6.4 ± 0.1	52 ± 1
	45.0	13.6 ± 0.2		
	55.0	18.9 ± 0.1		
4-Cl	35.0	12.1 ± 0.1	6.4 ± 0.1	51 ± 1
	45.0	17.4 ± 0.1		
	55.0	24.4 ± 0.1		

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Notes

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11. Activation enthalpy-entropy compensation phenomenon is prevailing one, however this phenomenon did not observed in the reaction studied.

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