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Pyridinolysis of Phenyl-Substituted Phenyl Chlorophosphates in Acetonitrile

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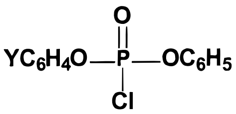
The kinetics and mechanism of the reactions of phenyl-substituted phenyl chlorophosphates, **I**, with pyridines in acetonitrile are investigated at 25.0 °C. The rates are much faster and the transition state is much earlier on the reaction coordinate with smaller β_X (0.16−0.18) and smaller negative β_{XY} (−0.011) values than those for the corresponding reactions with anilines. The vertical approach of the pyridine ring to an apical position of the trigonal bipyramidal transition state enables the $p_\pi - d_\pi$ overlap between the π orbital of pyridine and an empty d-orbital of phosphorus with less steric hindrance in a concerted process. The activation parameters are in line with the proposed mechanism.

Introduction

The mechanism of phosphoryl transfer from phosphate monoesters and diesters has been the subject of many recent investigations.[1] In particular a considerable amount of work has been devoted to elucidating the problem of whether the reaction proceeds through a pentacoordinate phosphorane intermediate or concertedly with a single transition state (TS).[2] Bourne and Williams[2b] and Skoog and Jencks[2a] measured the rates of the pyridinolysis of phosphorylpyridinium compounds and used the slopes, β_{nuc} and β_{lg}, of the Brønsted plots as a probe of the existence of intermediates in phosphoryl transfer reactions. They showed that the most likely mechanism is a concerted substitution reaction with an "exploded" TS with weak bonds to the attacking and leaving groups. In a previous work,[3] we investigated the mechanism of the aminolysis of phenyl-substituted phenyl chlorophosphates, **I**, with anilines in acetonitrile.



$$YC_6H_4O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle Cl}{|}}{P}}-OC_6H_5$$

I

The results were consistent with a concerted process, but rather unexpectedly the TS is predicted to be a late, productlike one in which both bond making and leaving group departure are extensive. Our prediction was based on the large negative cross-interaction constant,[4] ρ_{XY} and β_{XY} in eqs 1 and 2 where X and Y denote substituents in the nucleophile and substrate, **I**, respectively.

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \qquad (1a)$$

$$\rho_{XY} = \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y \qquad (1b)$$

$$\log(k_{XY}/k_{HH}) = \beta_X pK_{a(X)} + \beta_Y pK_{a(Y)} + \beta_{XY} pK_{a(X)} pK_{a(Y)} \qquad (2)$$

To gain further understanding of the mechanism of phosphoryl transfer, we carried out kinetic investigations of the pyridinolysis of **I** in acetonitrile at 25.0 °C. Specifically, we were interested in the difference in the TS structure of phosphoryl transfer reactions depending on the aniline (a primary amine) and pyridine (a tertiary amine) nucleophiles. We varied both the substituents X in the pyridine (p-NH$_2$, p-CH$_3$, H, m-CH$_3$CO, p-CH$_3$CO, and p-CN) and Y in **I** (Y = p-OCH$_3$, p-CH$_3$, H, p-Cl, and p-CN). Cross-interaction constants, ρ_{XY} and β_{XY} in eqs 1 and 2, have been determined.

Results and Discussion

A clean second-order kinetics according to eq 3 was obtained throughout this work; k_0 is the rate constant in the absence of pyridine nucleophile ($k_0 = 0$), and [N] is the pyridine concentration.

$$k_{obs} = k_0 + k_2[N] \qquad (3)$$

The second-order rate constants, k_2, obtained as the slope in eq 3 are summarized in Table 1. In general, the trends of rate changes with substituents X and Y are in accord with those expected from a typical nucleophilic substitution reaction with negative charge development at the reaction center (P) in the TS. The rates are much faster for the pyridinolysis than those for the aminolysis with isobasic anilines; e.g., for Y = H, $k_2 = 13.5 \times 10^{-2}$ M^{-1} s^{-1} (at 25.0 °C) and 10.7×10^{-3} M^{-1} s^{-1} (at 55.0 °C)[3] for the reactions with pyridine (X = H, pK_a = 5.21) and

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[1] See for example: Thatcher, G. R. J.; Luger, R. K. *Adv. Phys. Org. Chem.* **1989**, *25*, 99.

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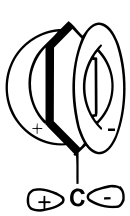
Table 1. Second-Order Rate Constants ($k_2 \times 10^2$ dm^3 mol^{-1} s^{-1}), Hammett and Brønsted Constants, and Cross-Interaction Constant for the Reactions of Phenyl Y-Substituted Phenyl Chlorophosphates with X-Substituted Pyridines in Acetonitrile at 25.0 °C

		Y					
X	pK_a^{a}	*p*-OCH$_3$ 10.21^b	*p*-CH$_3$ 10.26	H 9.99	*p*-Cl 9.41	*p*-CN 7.97	ρ_Y^{c}
p-NH$_2$	9.12	35.5	42.7	57.5	85.1	178	0.75 ± 0.01^d (0.999)^e
p-CH$_3$	6.03	12.6	15.5	20.0	28.1	56.2	0.69 ± 0.01 (0.999)
H	5.21	8.31	10.2	13.5	17.8	35.5	0.67 ± 0.03 (0.997)
m-CH$_3$CO	3.10	4.37	5.13	6.31	8.32	15.8	0.59 ± 0.02 (0.998)
p-CH$_3$CO	2.83	3.55	4.17	5.37	7.08	12.6	0.58 ± 0.01 (0.999)
p-CN	1.86	2.45	2.95	3.72	4.68	8.32	0.55 ± 0.02 (0.997)
ρ_X^{c}		−0.86 ± 0.02^d (0.999)^e	−0.87 ± 0.02 (0.999)	−0.89 ± 0.02 (0.999)	−0.94 ± 0.03 (0.998)	−1.00 ± 0.02 (0.999)	ρ_{XY}^{f} = −0.15 ± 0.03 (0.999)
β_X		0.16 ± 0.005^d (0.998)^e	0.16 ± 0.005 (0.998)	0.16 ± 0.003 (0.999)	0.17 ± 0.004 (0.999)	0.18 ± 0.005 (0.998)	

[a] Values at 25 °C in water were taken from Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591 and Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834. [b] pK_a values were taken from Albert, A.; Serjeant, E. P. *Determination of Ionization Constants*; Chapman and Hall: London, 1984; p 145. [c] σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. [d] Standard deviation. [e] Correlation coefficient. [f] Obtained by multiple regression analysis using 30 k_2 values.

aniline (X = *p*-OMe, pK_a = 5.34), respectively. This large difference in the rate may be due to resonance energy gain from the benzyl cation type π-complex (**II**) formation of pyridine with an empty d-orbital of the phosphorus atom (**III**) as suggested by Dewar.[5] This type of π-complex is not possible with aniline nucleophiles because the lone pair on the amino nitrogen is a p-type so that the horizontal π-cloud of the ring overlaps with the d-orbital of P marginally. Furthermore, since the attacking and leaving groups occupy apical positions of the trigonal bipyramidal (TBP) structure of a pentacoordinate TS or intermediate,[1] the horizontal approach of the aniline ring should cause excessive steric hindrance in contrast to a much less steric effect in the vertical approach of the pyridine ring, **III**. A similar but much smaller rate ratio was noted in the aminolysis of phosphorylpyridinium compounds; for nucleophiles of pK_a = 5, pyridines were 16-fold more reactive than primary amines with the same leaving group.[2a] The Hammett ρ_X (ρ_{nuc}) and ρ_Y values are shown in Table 1. The Brønsted β_X (β_{nuc}) values are obtained by correlating log k_2(MeCN) with pK_a(H$_2$O). This procedure is justified since our theoretical as well as experimental results indicated that although the pK_a(MeCN) values of the structurally similar amines are uniformly greater by 7.2 pK_a units than the pK_a(H$_2$O) values, the two vary in parallel with near unity slopes (1.02 at the IPCM/B3LYP/6-31G*//B3LYP/6-31G* level of theory[6] and 1.05 experimentally[7]). We note that the magnitudes of both ρ_X (−0.86 to −1.00) and β_X (0.16−0.18) in Table 1 are considerably smaller than the corresponding values for the aminolysis of **I** with anilines (ρ_X = −3.42 to −4.63 and β_X = 1.24−1.68).[3] The much smaller β_X values suggest a much smaller degree of bond formation with pyridines than with anilines in the TS. In fact, the size of β_X is similar to those for the reactions of pyridines and primary amines, β_X = 0.17 and 0.19 with phosphorylated 3-methoxypyridine and β_X = 0.22 and 0.28 with phosphorylated 4-morpholinopyridine.[2a] These small slopes show that the TS is earlier on the reaction coordinate in a concerted process, resembling the attacking amine more closely than a protonated amine, and



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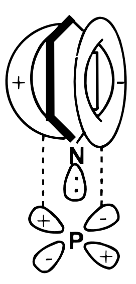

III

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(7) The experimental pK_a values of 22 alkyl, alicyclic amines and pyridine gave the correlation pK_a(MeCN) = 1.05pK_a(H$_2$O) + 7.20, r = 0.972, n = 22. Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 45.

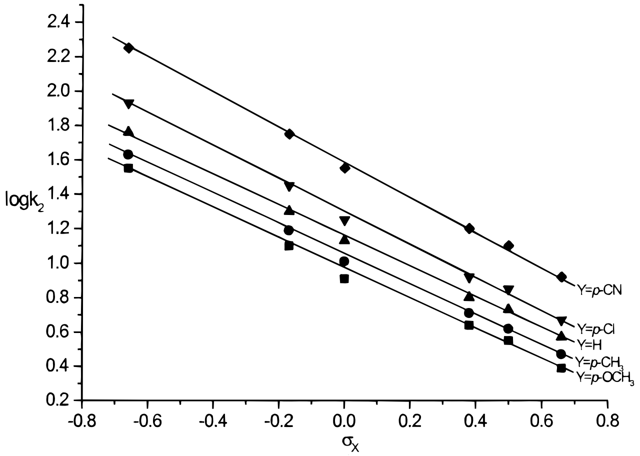
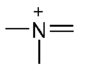


Figure 1. Hammett plots for the pyridinolysis of phenyl-substituted phenyl chlorophosphates in acetonitrile at 25.0 °C.

suggest there is little bond formation between the amine and phosphorus in the TS. As a result of the early TS with little positive charge development on the nitrogen of pyridines, there were no positive deviations for the π-acceptor (X = p-CH_3CO and p-CN) in the Hammett plots, Figure 1. These deviations are known to result from the exalted basicity (or nucleophilicity) due to a π-donor effect of such substituents under the strong cationic charge of azonium ion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formation in the pyridines.[8]

The ρ_Y values ($\rho_Y = 0.55-0.75$ for $\Delta pK_{a(X)} = 7.06$) in Table 1 are similar but vary very little with the basicity of the nucleophile compared to those with anilines ($\rho_Y = 0.22-0.87$ for $\Delta pK_{a(X)} = 1.36$). This supports the idea that the TS is early with little bond formation of the nucleophile and little bond cleavage of the leaving group in a backside attack S_N2 reaction of the pyridine nucleophile on the phosphorus atom with concerted departure of the chloride leaving group. The much earlier TS suggested for the pyridinolysis by the smaller magnitude of β_X and positive ρ_Y values is in contrast to the later TS proposed for the reactions of **I** with anilines.[3] However, a slower rate (with anilines) with a later TS is in accord with the Bell−Evans−Polanyi (BEP) principle[9] and also in accord with the experimentally based prediction that a tighter bond formation is obtained for a sterically hindered and hence high activation barrier reaction.[4c,10]

The proposed mechanism is supported by the small negative cross-interaction constant, $\rho_{XY} = -0.15$ ($\beta_{XY} = -0.011 \pm 0.005$, $r = 0.993$, $n = 30$), and also by the failure[11] of the reactivity−selectivity principle, which asserts that the higher rates lead to lower selectivity parameters.[12] For the reactions with anilines, the ρ_{XY} (and β_{XY}) value was much more negative, $\rho_{XY} = -1.31$ ($\beta_{XY} = -0.18 \pm 0.05$, $r = 0.994$, $n = 20$). The negative sign of ρ_{XY} (β_{XY})[13] is consistent with a concerted process, and the small magnitude is an indication of a small degree of bond formation. A positive ρ_{XY} value is predicted and has been observed for the stepwise acyl transfer with rate-limiting breakdown of a tetrahedral intermediate.[14] Young and Jencks[15] reported a ρ_{XY} value of −0.95 and the corresponding β_{XY} value of −0.045 for the S_N2 reactions of benzyl chlorides with anilines in ethanol. The magnitude of this ρ_{XY} (and β_{XY}) value is near that of the average for normal S_N2 reactions, $\rho_{XY} = -0.7$,[4b] and is an intermediate value between those for the reactions of **I** with anilines and pyridines.

Table 2. Activation Parameters[a] for the Reactions of Phenyl Y-Substituted Phenyl Chlorophosphates with X-Substituted Pyridines in Acetonitrile

Y	X	temp/ °C	$k_2 \times 10^2$/ (m^{-1} s^{-1})	$\Delta H^‡$/ (kcal mol^{-1})	$\Delta S^‡$/ (cal mol^{-1} K^{-1})
p-Cl	p-NH_2	5	33.8		
		15	56.2	7.0 ± 0.2[b]	35 ± 1[b]
		25	85.1		
p-OCH_3	p-CH_3	5	3.60		
		15	7.10	10.0 ± 0.2	30 ± 1
		25	12.6		
H	H	5	3.71		
		15	9.40	10.2 ± 0.2	28 ± 1
		25	13.5		

[a] Calculated by the Eyring equation. [b] Standard deviation.

The activation parameters, $\Delta H^‡$ and $\Delta S^‡$, in Table 2 are also consistent with the concerted process proposed. The magnitudes of $\Delta H^‡$ and $\Delta S^‡$ are in the range of those for typical S_N2 reactions.[16]

In summary, the pyridinolysis of phenyl-substituted phenyl chlorophosphates, **I**, in acetonitrile at 25.0 °C proceeds concertedly (S_N2) with an early TS in which the extent of both bond formation and leaving group departure is small. The rates are much faster than those of the corresponding reactions with anilines due to the resonance stabilization of $p_\pi-d_\pi$ overlap between the π-orbital of the pyridine ring and the empty d-orbital of the phosphorus atom in the TS. Consistent with the PES principle, the much faster rates lead to a much earlier TS with much smaller magnitudes of β_X (β_{nuc}) and ρ_{XY} (β_{XY}). The negative sign of ρ_{XY} (and β_{XY}) is consistent with the concerted process proposed. The activation parameters also support the mechanism proposed.

Experimental Section

Materials. Aldrich GR grade pyridines were used without further purification. All other materials were as reported previously.[3]

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[13] A similar cross-interaction constant, $p_{xy'}$, was defined by Jencks et al.; the two, ρ_{XY} and $p_{xy'}$, have opposite signs, and their magnitudes are related by $\rho_{XY} = \rho_{e(X)}p_{xy'}$, where $\rho_{e(X)} = \Delta pK_X/\sigma_X$.[4b] (a) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7448. (b) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

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Rate Constants. Rate constants were determined as described previously.[3]

Product Analysis. Phenyl *p*-methoxyphenyl chlorophosphate was reacted with an excess of *p*-methylpyridine with stirring for more than 15 half-lives at 25.0 °C in acetonitrile. The product mixture was treated for workup with ether and water. After workup, anhydrous $MgSO_4$ was added, and the solvent was evaporated under reduced pressure after filtration. The spectral data after column chromatography (silica gel, 20% ethyl acetate + 80% *n*-hexane) are the following.

$(PhO)(p\text{-}OCH_3{-}C_6H_4O)P({=}O)N^+C_5H_4\text{-}p\text{-}CH_3$: semisolid; yield 67%; ^1H NMR (200 MHz, $CDCl_3$), δ 2.1−2.2 (3H, s, CH_3), 3.7−3.8 (3H, s, CH_3O), 6.7−6.9 (4H, s, C_5H_4N), and 7.1−7.3 (C_6H_5 + C_6H_4); IR ν_{max}(neat) 3077 (CH, aromatic), 2834 (CH, aliphatic), 1609, 1507, and 1093 ($P{-}O{-}C_6H_5$), and 1249 ($P{=}O$); MS *m*/*z* 355 (M^+, molecular ion peak) with conditions of dilution factor 1, retention time 17.083 min, and base peak 309.10.

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