Reaction Mechanism and Structure of Transition State Determined from Analysis of Brønsted β_{nuc} for Aminolysis of 4-Nitrophenyl Diphenylphosphinate

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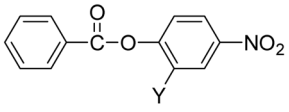
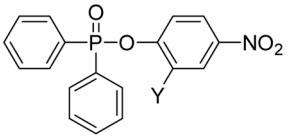
Useful information on reaction mechanism can be obtained from analysis of Brønsted-type plots. Curved Brønsted-type plots often found for reactions of esters possessing a good leaving group (*e.g.*, 2,4-dinitrophenoxide) have been taken as evidence for a change in the rate-determining step (RDS) of a stepwise mechanism.[1-10] In fact, a curved Brønsted-type plot has been reported for reactions of 2,4-dinitrophenyl benzoate (**1**) with a series of alicyclic secondary amines, *i.e.*, the β_{nuc} value decreases from 0.74 to 0.34 as the amine basicity increases.[4a] In contrast, the corresponding reactions of 4-nitrophenyl benzoate (**2**) resulted in a linear Brønsted-type plot with β_{nuc} = 0.88 in the pK_a range 5.95-11.02.[4b] Thus, it has been concluded that the aminolyses of **1** and **2** proceed through a stepwise mechanism and the RDS changes in the reactions of **1** but not in the reactions of **2** in that pK_a range.[4a,b]



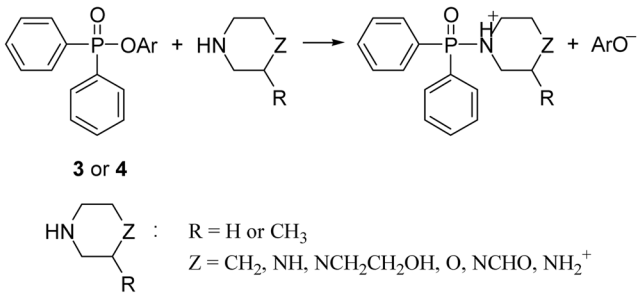
1 (Y = NO_2), **2** (Y = H)



3 (Y = NO_2), **4** (Y = H)

Certain organophosphorus compounds have been used as insecticides or chemical warfare, *e.g.*, paraoxon (4-nitrophenyl diethyl phosphate), parathion (4-nitrophenyl diethyl thiophosphate), sarin (isopropoxy methylphosphoryl fluoride), etc.[11-16] Various methods have been developed to destroy these toxic compounds efficiently in mild conditions (*e.g.*, use of highly reactive α-effect nucleophiles[11-13] or various metal ions as Lewis acid catalysts).[14-16] However, only a few reports are available for aminolysis of phosphoryl and related compounds.[10,17,18]

Aminolysis of organophosphorus compounds has been reported to proceed through a concerted or a stepwise mechanism. From a systematic study of leaving-group effect, medium effect, and activation parameters, Cook *et al.* have drawn a conclusion that aminolysis of aryl diphenylphosphinates and related compounds in CH_3CN proceeds through a zwitterionic intermediate with its breakdown being RDS.[17] In contrast, Lee *et al.* have proposed that pyridinolysis of aryl phenyl chlorophosphates proceeds through a concerted mechanism on the basis of linear



3 or **4**

HN Z R : R = H or CH_3; Z = CH_2, NH, NCH_2CH_2OH, O, NCHO, NH_2^+

Scheme 1

Brønsted-type plots with small β_{nuc} values (*e.g.*, β_{nuc} = 0.16-0.18).[18] We have recently performed aminolyses of 2,4-dinitrophenyl diphenylphosphinate (**3**) and its related compounds, and concluded that the reactions proceed through a concerted mechanism on the basis of linear Brønsted-type plots with β_{nuc} = 0.38-0.52 and excellent Yukawa-Tsuno correlation with an r value of *ca.* 0.3.[10]

We have extended our study to reactions of 4-nitrophenyl diphenylphosphinate (**4**) with a series of alicyclic secondary amines (Scheme 1) to investigate the reaction mechanism by comparing the kinetic results obtained from the current study with those reported previously for the corresponding reactions of **2**.[4b] The current kinetic data have also been compared with those reported recently for the reactions of 2,4-dinitrophenyl diphenylphosphinate (**3**)[10] to investigate the effect of leaving group basicity on reactivity and reaction mechanism.

Results and Discussion

All reactions obeyed first-order kinetics with quantitative liberation of 4-nitrophenoxide ion and/or its conjugate acid. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. It is estimated from replicate runs that the uncertainty in the rate constants is less than ± 3%.

As shown in Figure 1, the plots of k_{obsd} *vs.* amine concentration are linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent. Thus, the rate equation can be given as eq. (1), and the second-order rate constants (k_N) for reactions of **4** have been determined from the slope of the linear plots. The k_N values

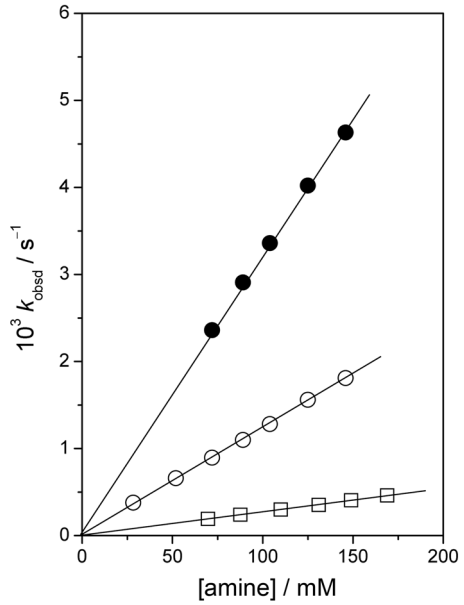


Figure 1. Plots of k_{obsd} *vs.* [amine] for reactions of 4-nitrophenyl diphenylphosphinate (**4**) with piperidine (●), piperazine (○), and morpholine (□) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

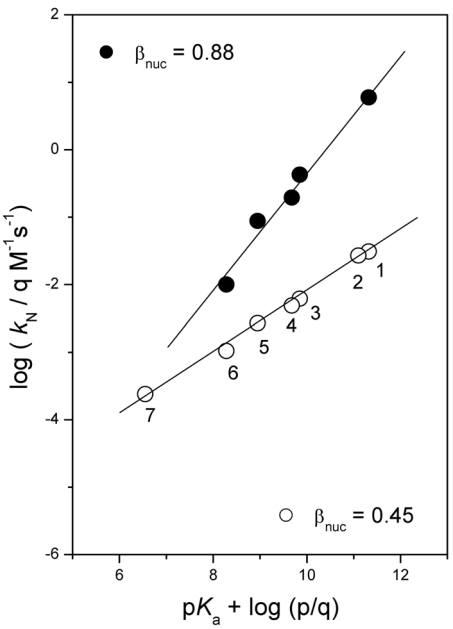


Figure 2. Brønsted-type plots for the reactions of 4-nitrophenyl benzoate **2** (●) and 4-nitrophenyl diphenylphosphinate **4** (○) with alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

determined in this way are summarized in Table 1 together with the k_N values for the corresponding reactions of **2** and **3** for comparison purpose.

$$\text{Rate} = k_{obsd}[\text{substrate}], \text{ where } k_{obsd} = k_N[\text{amine}] \quad (1)$$

Effect of Changing Electrophilic Center from C=O to P=O. Table 1 shows the effect of changing the electrophilic center from C=O to P=O on reactivity, *i.e.*, phosphinate **4** is less reactive than benzoate **2** for a given amine. It is noted that the rate-constant ratio (k_N^2/k_N^4) decreases as the basicity of attacking amine decreases, *e.g.*, the k_N^2/k_N^4 ratio decreases from 194 to 39.9 and 9.52 as the pK_a of the conjugate acid of amines decreases from 11.02 to 9.38 and 7.98, respectively.

Figure 2 demonstrates the effect of changing electrophilic center from C=O to P=O on reaction mechanism as a function of amine basicity. The Brønsted-type plots for the reactions of both **2** and **4** are linear. However, the slope of the linear plots is much smaller for the reactions of **4** than for those of **2**, *i.e.*, β_{nuc} = 0.88 and 0.45 for the reactions of **2** and **4**, respectively.

The magnitude of β_{nuc} values has been used as a measure of reaction mechanism: β_{nuc} = 0.8 ± 0.1 for reactions which proceed through an intermediate with its breakdown being the RDS, while β_{nuc} = 0.2 ± 0.1 when formation of an intermediate is the RDS.[1-10] In fact, the reactions of **2** were concluded to proceed through a stepwise mechanism in which breakdown of the intermediate is the RDS.[4b] On the other hand, reactions which proceed through a concerted mechanism have often been reported to result in a β_{nuc} value of 0.5 ± 0.1.[1-10] Accordingly, one can suggest that the current aminolysis of **4** proceeds through a concerted mechanism on the basis of the fact that β_{nuc} = 0.45.

Figure 2 also demonstrates that **4** is less reactive than **2**. Modification of electrophilic center from C=O to P=O would cause a change in the electrophilicity of substrates **2** and **4**. If a change in the electrophilicity of **2** and **4** were responsible for the reactivity difference, one might expect that the k_N^2/k_N^4 ratio should have been independent of the basicity of incoming amines. However, in fact, the k_N^2/k_N^4 ratio decreases as the incoming amine becomes weakly basic, indicating that the reactivity difference between **2** and **4** is not caused solely by a change in the electrophilicity upon modification of the electrophilic center from C=O to P=O. It is apparent that the difference in reaction mechanism as discussed above also contributes to the difference in reactivity between **2** and **4**.

Table 1. Summary of Second-order Rate Constants (k_N, $M^{-1}s^{-1}$) for Reactions of 4-Nitrophenyl Benzoate (**2**), 2,4-Dinitrophenyl Diphenylphosphinate (**3**), and 4-Nitrophenyl Diphenylphosphinate (**4**) with Alicyclic Secondary Amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

Entry	Amine	pK_a [a]	$10^2 k_N$ / $M^{-1}s^{-1}$		
			2 [b]	**3** [c]	**4**
1	piperidine	11.02	594	419	3.06
2	3-methylpiperidine	10.80	–	429	2.69
3	piperazine	9.85	85.1	234	1.22
4	1-(2-hydroxyethyl)-piperazine	9.38	19.5	93.9	0.489
5	morpholine	8.65	8.76	57.3	0.269
6	1-formylpiperazine	7.98	1.00	33.2	0.105
7	piperazinium ion	5.95	–	7.09	0.0238

[a] The pK_a data in 20 mol % DMSO taken from ref 4a. [b] Data taken from ref 4b. [c] Data taken from ref 10a.

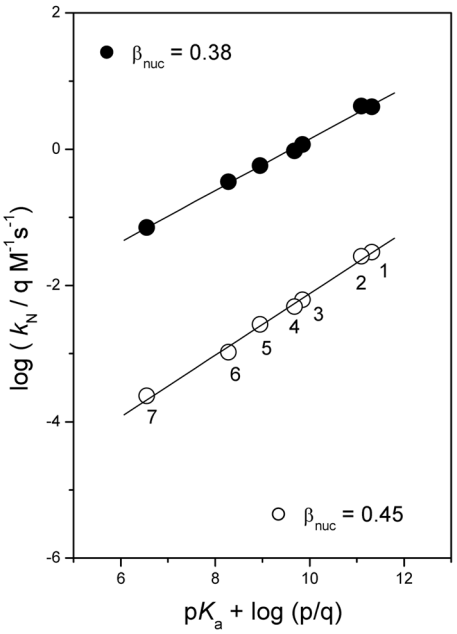


Figure 3. Brønsted-type plots for reactions of 2,4-dinitrophenyl diphenylphosphinate **3** (●) and 4-nitrophenyl diphenylphosphinate **4** (○) with alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

Effect of Changing Leaving-group Basicity on Transition-state Structure. To investigate the effect of changing the leaving group from 2,4-dinitrophenoxide to 4-nitrophenoxide on mechanism, the Brønsted-type plot for the current reactions of **4** has been compared with that reported previously for the corresponding reactions of **3** which have been concluded to proceed through a concerted mechanism. As shown in Figure 3, the Brønsted-type plots are linear with typical β_{nuc} values for reactions proceeding through a concerted mechanism.

As expected from the difference in the leaving-group basicity (*e.g.*, the pK_a of 4-nitrophenol and 2,4-dinitrophenol = 7.14 and 4.11, respectively), substrate **4** is much less reactive than **3** regardless of the basicity of the attacking amines. It is noted that the less reactive **4** exhibits a slightly larger β_{nuc} value (0.45) than the more reactive **3** (0.38). Thus, the current result is consistent with the reactivity-selectivity principle (RSP).[19]

The magnitude of β_{nuc} values has often been taken as a relative degree of bond formation between the electrophilic center and the incoming nucleophile in the transition state (TS).[19] The fact that reactions of **4** results in a slightly larger β_{nuc} value than those of **3** indicates that the degree of bond formation in the TS is slightly more advanced for the former reactions than for the latter reactions. Thus, one can suggest that modification of the leaving group from 2,4-dinitrophenoxide to the more basic 4-nitrophenoxide influences TS structure but not the reaction mechanism for aminolyses of phosphinates **3** and **4** on the basis of the magnitude of β_{nuc} values.

In summary, analysis of the Brønsted-type plots for the aminolyses of **2**, **3** and **4** has allowed us to conclude the following: (1) The reactions of **3** and **4** proceed through a concerted mechanism, while the corresponding reactions of **2** proceed through an intermediate with its breakdown being the RDS. (2) Changing the leaving group from 2,4-dinitrophenoxide to 4-nitrophenoxide does not affect the reaction mechanism but influences the structure of TS, *i.e.*, the degree of bond formation in the TS is slightly more advanced for the reactions of the less reactive **4** than for those of the more reactive **3** in accord with the RSP.

Experimental Section

Materials. Compound **4** was prepared as reported previously.[10a] Other chemicals used were of the highest quality available. The reaction medium was H_2O containing 20 mol % DMSO. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV-vis spectrophotometer equipped with a constant temperature circulating bath to maintain the temperature in the reaction cell at 25.0 ± 0.1 °C. The reaction was followed by monitoring the appearance of the leaving 4-nitrophenoxide ion (or 4-nitrophenol for the reaction with piperazinium ion). All the reactions were carried out under pseudo-first-order conditions in which nucleophile concentrations were at least 20 times greater than the substrate concentration. The amine stock solution of *ca*. 0.2 M was prepared by dissolving two equiv of amine and one equiv of standardized HCl solution to keep the pH constant in this self-buffered solution. All solutions were prepared freshly just before use under nitrogen, and transferred by gas-tight syringes. Typically, reactions were initiated by adding 5 μL of a 0.02 M solution of the substrate in CH_3CN by a 10 μL syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostatted reaction mixture made up of solvent and aliquot of the nucleophile stock solution.

Product Analysis. 4-Nitrophenoxide (and/or its conjugate acid) was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectrum at the end of reaction with the authentic sample under the experimental condition.

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