Nucleophilic Substitution Reactions of Diethyl 4-Nitrophenyl Phosphate Triester: Kinetics and Mechanism

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Received 5 May 2011; revised 1 August 2011; accepted 3 August 2011

DOI 10.1002/kin.20605 Published online 22 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: The reactions of diethyl 4-nitrophenyl phosphate (1) with a series of nucleophiles: phenoxides, secondary alicyclic (SA) amines, and pyridines are subjected to a kinetic study. Under excess of nucleophile, all the reactions obey pseudo-first-order kinetics and are first order in the nucleophile. The nucleophilic rate constants (k_N) obtained are pH independent for all the reactions studied. The Brønsted-type plot (log k_N vs. pK_a nucleophile) obtained for the phenolysis is linear with slope $\beta = 0.21$; no break was found at pK_a 7.5, consistent with a concerted mechanism. The Brønsted-type plots for the SA aminolysis and pyridinolysis are linear with slopes $\beta = 0.39$ and 0.43, respectively, also suggesting concerted processes. The concerted mechanisms for the latter reactions are proposed on the basis of the lack of break in the Brønsted-type plots and the instability of the hypothetical pentacoordinate intermediates formed in these reactions. © 2011 Wiley Periodicals, Inc. Int J Chem Kinet 43: 708–714, 2011

INTRODUCTION

The importance of phosphate esters in nature has been one of the reasons for the continued interest in the study of phosphoryl transfer mechanisms [1,2]. Reactions

Contract grant number: 08/2009

such as hydrolysis and other nucleophilic substitution reactions of phosphoesters are involved in important biological processes, and extensive studies have been developed in attempts to understand the mechanisms of these reactions [3–6]. These compounds show different reactivity and mechanisms depending primarily on their alkylation or arylation state (mono, di, or triester) and the nature of the nucleophile. Some triester derivatives that contain both alkyl and aryl substituents show three possible reaction pathways: nucleophilic attack on the phosphorus center, aliphatic carbon, and aromatic carbon. These three pathways were detected in the hydrolysis of *O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate [7,8].

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Contract grant sponsor: FONDECYT of Chile

Contract grant number: 1100640

Contract grant sponsor: Vicerrectoría de Investigación (VRI) of Pontificia Universidad Católica de Chile

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Nevertheless, in the reactions of the same substrate with several O- and N-based nucleophiles, and also for bis(2,4-dinitrophenyl)phosphate and methyl 2,4dinitrophenyl phosphate diester, only two paths, nucleophilic attack on phosphorus and the aromatic carbon, were detected [5,9–11]. On the other hand, attack only on the P center was observed for the reactions of aryl dimethylphosphinothioate and 2-(2,4'-dinitrophenyl)-2-oxo-1,3,2-dioxaphosphinanes with different phenoxide ions and some O- α nucleophiles [3,11–13]. It is known that when the nucleophilic substitution reactions occur at the P center, they can proceed by two main types of mechanism: the stepwise mechanism, involving a trigonal bipyramidal pentacoordinate intermediate, and the concerted mechanism, through a single pentacoordinate transition state [3].

To establish the mechanism of a reaction of phosphoryl transfer from kinetic results, linear free energy relationships have been utilized (i.e., Brønsted and/or Hammett equations). The slope value of the Brønstedtype plot (β) seems to depend on both the nucleophile nature and the alkylation state of the phosphate ester derivative [4,5]. For example, linear Brønstedtype plots have been found for the concerted reactions of 2,4-dinitrophenyl diphenylphosphinate with secondary alicyclic (SA) amines in dimethyl sulfoxide (DMSO)-H₂O (20:80 mol%), with $\beta = 0.38$ [14–16] and the pyridinolysis of methyl S-aryl thiophosphate and methyl aryl phosphate diesters in the same solvent mixture, with $\beta = 0.42$ and 0.56, respectively [17]. The concerted anilinolysis of dimethyl and diethyl chlorophosphates and chlorothionophosphates and aryl ethyl chlorothionophosphate in acetonitrile shows larger Brønsted slopes, $\beta = 0.96-1.1$ [18-20]. Nonetheless, much smaller Brønsted slopes have been reported for the concerted pyridinolysis of substituted phenyl chlorophosphates in acetonitrile, $\beta = 0.16-0.18$ [21].

These β values are much smaller than those obtained for the anilinolysis reactions of the same substrates [20]; nevertheless, they are similar to those found in the concerted pyridinolysis and SA aminolysis of phosphorylated 3-methoxypyridine and phosphorylated 4-morpholinopyridine, with $\beta = 0.17$ –0.19 and 0.22–0.28, respectively [22,23].

On the other hand, when the nucleophile is an anion, values of $\beta = 0.46-0.7$ have been found for the phenolysis of aryl diphenylphosphinate, aryl dimethylphosphinothionate, and bis(4-nitrophenyl) phenyl phosphate. These values are consistent with a single transition-state mechanism [24–26]. It is noteworthy that for the reactions of aryl dimethylphosphinothionate [24], Brønsted β values of 0.47 and β_{1g} of -0.52 have been found for the reactions with phenoxides, and

International Journal of Chemical Kinetics DOI 10.1002/kin

 β values of 0.08 and β_{1g} of -0.54 for the reactions with alkoxides as nucleophiles. For the phenolysis of substituted phenyl diphenyl phosphate in aqueous media at 25°C, small values of β (0.12) have been obtained [13]. Nonetheless, despite the difference in the β values, all these reactions have been reported to proceed by a concerted mechanism.

Most of the available information on the mechanisms of the phosphoryl group transfer refers to monoester or diester phosphates; however, the information on the mechanism of nucleophilic substitution reactions of triester derivatives in aqueous solution is scarce. To gain further understanding on the mechanism of phosphoryl transfer of triester derivatives, we carried out a kinetic investigation of the aminolysis (SA amines), pyridinolysis, and phenolysis of diethyl 4-nitrophenyl phosphate triester (1) in 44 wt% ethanolwater at $25.0 \pm 0.1^{\circ}$ C and an ionic strength of 0.2 M. The products analysis, by ultraviolet-visible (UV-vis) and high-performance liquid chromatography (HPLC) techniques, shows that the nucleophilic attack is on the phosphoryl center, the only reaction pathway being the P-OAr cleavage through the S_N2(P) mechanism. Namely, no nucleophilic aromatic substitution was found for these reactions.

EXPERIMENTAL

Materials

A series of SA amines, pyridines, and phenols were recrystallized, sublimated, or redistilled before use. Phosphate **1** was from a commercial source and used as purchased.

Kinetic Measurements

These were performed spectrophotometrically (diode array) in the range 300–500 nm, by following the appearance of 4-nitrophenoxide anion, by means of a Hewlett–Packard 8453 instrument. The reactions were carried out in 44 wt% ethanol–water at $25.0 \pm 0.1^{\circ}$ C and an ionic strength of 0.2 M (maintained with KCl). Borate buffer was used in some reactions. At least a 10-fold excess of total nucleophile over the substrate was employed. The initial concentration of the substrate was 8×10^{-5} M in all reactions. Pseudo-first-order rate coefficients (k_{obsd}) were found throughout, and most of them were determined by the initial rate method [27]. The experimental conditions of the

reactions and the k_{obsd} values obtained are presented in Tables S1–S16 of the Supporting Information.

pK_a Values

The pK_a values for the phenols, SA amines, and pyridines were taken from [28–30]. These pK_a values were determined spectrophotometrically by the reported method [31].

Product Studies

For the phenolysis, SA aminolysis, and pyridinolysis reactions of phosphate 1, one of the products was identified as 4-nitrophenoxide. These analyses were carried out by UV-vis spectrophotometry, by comparison of the UV-vis spectra after completion of these reactions with those of authentic samples under the same experimental conditions. In the reactions of phenol and morpholine with 1, the HPLC analysis showed the presence of 4-nitrophenoxide (retention time = 3.3 min, $\lambda_{\text{max}} =$ 400 nm) and diethyl phenyl phosphate and diethyl morpholinophosphate, respectively (retention time = 5.7and 1.9 min, $\lambda_{max} = 210$ and 258 nm), during the time of the kinetic measurements. This was achieved by comparison of the HPLC spectra with that of the product of the reaction of diethyl chlorophosphate with phenol and morpholine, respectively. The formation of the corresponding products from attack on the aromatic carbon moiety was not detected by HPLC analysis (less than 1%), being therefore disregarded (or considered insignificant) as one of the reaction products.

HPLC conditions: diode array detector provided with LiChroCART^(R) 250-mm HPLC-RP-18e (5 μ m) (Merck, Darmstadt, Germany), mobile phase 50% (v/v) CH₃CN–phosphate buffer (0.01 M, pH 7.00), and a flow rate of 1.0 mL/min.

RESULTS AND DISCUSSION

The rate law obtained for most of the reactions under investigation is given by Eq. (1), where P is 4-nitrophenoxide anion, S represents the substrate (1),

and k_{obsd} is the pseudo-first-order rate coefficient (excess of nucleophile over the substrate was used):

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = k_{\mathrm{obsd}}[\mathrm{S}] \tag{1}$$

The plots of k_{obsd} against free nucleophile concentration are linear, according to Eq. (2), where k_0 is the rate coefficient for solvolysis of the substrate and k_N is the nucleophilic rate coefficient for SA aminolysis, pyridinolysis, or phenolysis of the substrate. The values of k_0 were much lower than those of the k_N [free nucleophile] term in Eq. (2):

$$k_{\text{obsd}} = k_0 + k_{\text{N}}[\text{free nucleophile}]$$
 (2)

The experimental conditions and the values of k_{obsd} obtained for the reactions of **1** with the different series of nucleophiles are presented in Tables S1–S16 of the Supporting Information. The values found for the nucleophilic rate constants k_N for the reactions of **1** with SA amines, pyridines, and phenoxides are presented in Tables I, II, and III, respectively.

Figure 1 shows the Brønsted-type plots for SA aminolysis, pyridinolysis, and phenolysis of the substrate. The k_N values for the reactions of SA amines, as well as those of the pK_a of the conjugate acids of the SA amines, were statistically corrected with q = 2 for piperazine (q = 1 for all the other SA amines) and p = 2 for all the conjugate acids of the amines [32]. For all the phenoxides and pyridines used in this study, p = 1 and q = 1. The parameter q is the number of equivalent basic sites in the free amine, and p is the number of equivalent dissociable protons in the conjugate acid of the amine [33].

Phenolysis Reaction

The linear Brønsted-type plot obtained for the phenolysis of **1** shows a slope (β) value of 0.21 ± 0.02, $R^2 = 0.96$. Considering that there is a large scatter of β values described for the reactions between phosphates and oxygenated nucleophiles, the β value found for

Table I Values of pK_a for the Conjugate Acids of SA Amines and k_N Values for the Reactions of SA Amines with Diethyl 4-Nitrophenyl Phosphate $(1)^a$

SA Amine	pK _a	$10^3 k_{\rm N} ({\rm s}^{-1}{\rm mol}^{-1}{\rm dm}^{-3})$	$10^5 k_0 ({\rm s}^{-1}{\rm mol}^{-1}{\rm dm}^{-3})$	R^2
Piperidine	10.82	0.09 ± 0.01	0.42 ± 0.08	0.97
Piperazine	9.71	0.06 ± 0.03	0.08 ± 0.02	0.96
1-(2-Hydroxyethyl)piperazine	9.09	0.02 ± 0.01	0.08 ± 0.01	0.99
Morpholine	8.48	0.01 ± 0.001	0.02 ± 0.01	0.92
1-Formylpiperazine	7.63	0.006 ± 0.001^{b}	0.12 ± 0.01	0.96

^{*a*}Both the p K_a and k_N values were determined in 44 wt% ethanol–water at 25°C and ionic strength of 0.2 M. ^{*b*}Borate buffer 0.05 M.

Pyridine Substituent	pK _a	$10^3 k_{\rm N} ({\rm s}^{-1} {\rm mol}^{-1} {\rm dm}^{-3})$	$10^5 k_0 ({\rm s}^{-1}{\rm mol}^{-1}{\rm dm}^{-3})$	R^2		
4-Oxy	11.5	0.43 ± 0.04	0.2 ± 0.2	0.93		
3,4-Diamino	9.45	0.03 ± 0.02	0.05 ± 0.01	0.96		
4-Dimethylamino	9.14	0.03 ± 0.01	0.07 ± 0.02	0.97		
4-Amino	8.98	0.02 ± 0.01	0.05 ± 0.02	0.95		
3,4-Dimethyl	5.68	0.0012 ± 0.0001^{b}	0.05 ± 0.01	0.97		

Table II Values of pK_a for the Conjugate Acids of Pyridines and k_N Values for the Reactions of Pyridines with Diethyl 4-Nitrophenyl Phosphate (1)^{*a*}

^{*a*}Both p K_a and k_N values were determined in 44 wt% ethanol–water at 25°C and ionic strength of 0.2 M (KCl). ^{*b*}Borate buffer 0.05 M.

Table III Values of pK_a for the Phenols and k_N Values for the Phenolysis of Diethyl 4-Nitrophenyl Phosphate (1)^a

Phenoxide Substituent	pK _a	$10^3 k_{\rm N} ({\rm s}^{-1}{\rm mol}^{-1}{\rm dm}^{-3})$	$10^6 k_0 ({\rm s}^{-1}{\rm mol}^{-1}{\rm dm}^{-3})$	R^2
4-OCH ₃	11.55	0.34 ± 0.01	5.6 ± 0.5	0.99
Н	11.16	0.15 ± 0.01	0.16 ± 0.08	0.96
4-Cl	10.47	0.15 ± 0.02	2.3 ± 0.1	0.93
4-CN	8.21	0.067 ± 0.004	1.9 ± 0.5	0.97
2,6-F ₂	7.82	0.044 ± 0.001^{b}	1.1 ± 0.1	0.98
2,3,4,5,6-F ₅	5.83	0.016 ± 0.001^b	1.0 ± 0.1	0.94

^{*a*}Both the p K_a and k_N values were determined in 44 wt% ethanol–water at 25°C and ionic strength of 0.2 M. ^{*b*}Borate buffer 0.05 M.

this reaction is not sufficient to discriminate between concerted or stepwise mechanisms. Nevertheless, if the phenolysis of **1** were stepwise, its Brønsted-type plot would be biphasic with a pK_a^0 (pK_a at the curvature center) of 7.5, corresponding to the pK_a value of 4-nitrophenol (under the reaction conditions) [34]. This is the pK_a at which the hypothetical pentacoordinate intermediate would break into reactants and products



Figure 1 Brønsted-type plots for the reactions of phenoxides (\blacktriangle), pyridines (o), and SA amines (\bullet) with phosphate **1** in 44 wt% ethanol–water at 25°C and an ionic strength of 0.2 M (KCl).

with equal rates [34–38]. The absence of curvature within the pK_a range of the nucleophiles employed is a conclusive proof that the mechanism of this reaction is concerted [34–38].

Moreover, a concerted phenolysis of 4-nitrophenyl diphenylphosphinate in water has been reported [19]. Therefore, the hypothetical pentacoordinate intermediate I is unstable and does not exist. It is known that the change of methyl to ethoxy destabilizes the intermediate due to the major "push" provided by the EtO group, and the concerted process is favored [39]. Therefore, it is reasonable to expect that the change of phenyl by EtO also destabilizes the intermediate. Moreover, the change of solvent, from water to 44 wt% ethanol–water, should further destabilize the anionic intermediate II.



Taking into account the above arguments and the product analysis study (see the Experimental section), the most probable mechanism for the phenolysis reactions of the title substrate is shown in Scheme 1.

SA Aminolysis Reaction

The value of the Brønsted slope obtained in the SA aminolysis of 1 ($\beta = 0.39 \pm 0.02$, $R^2 = 0.99$) is in agreement with those found in the concerted reactions of 4-nitrophenyl diphenylphosphinate with SA amines in DMSO–H₂O 20:80 mol% ($\beta = 0.38$) [15,16] and the concerted pyridinolyses of methyl S-aryl thiophosphate and methyl aryl phosphate diesters in the same solvent mixture, $\beta = 0.42$ and 0.56, respectively [17].

As mentioned above, the magnitude of the Brønsted slope alone is not sufficient to discriminate whether the mechanism of the reaction is concerted or stepwise [34,40–42]. Nevertheless, it is known that the pK_a^0 value for the stepwise aminolysis of esters and carbonates is ca. 2–4 pK_a units larger than that of the nucleofuge (aryloxide) [43–45]. Therefore, in the case of the reactions of **1** with SA amines, the ex-

pected pK_a^0 value would be 9.5–11.5, which is in the pK_a range of the nucleophiles studied. The lack of break in the Brønsted-type plot is a conclusive proof that the mechanism of this reaction is concerted [34,37,38].

On the other hand, a concerted anilinolysis of 4-nitrophenyl diphenylphosphinate in DMSO–H₂O 20:80 mol% has been reported [14]; therefore, the zwitterionic pentacoordinate intermediate **III** is unstable and does not exist. If the reaction of SA amines with **1** were stepwise, the hypothetical intermediate would be the zwitterionic pentacoordinate intermediate **IV**. The absence of curvature in the Brønsted-type plot, the product analysis (see the Experimental section), and the following discussion permit us to propose a concerted mechanism (Scheme 2) for the SA aminolysis of phosphate **1**.



Nu: SA amines or pyridines

Scheme 2



(i) The change of a phenyl group by EtO destabilizes the intermediate due to the greater "push" by EtO (see above) [39]. (ii) It is also known that in the aminolysis of carbonates, SA amines destabilize a tetrahedral intermediate, compared with isobasic anilines [35,36]. Therefore, it is reasonable that the same destabilizing effect would occur in a pentacoordinate intermediate (III). Considering the dielectric constant as a polarity measure, since III is unstable in aqueous 20 mol% DMSO ($\varepsilon = 74.3$ at 25°C) [46,47], the change to aqueous 44 wt% ethanol ($\varepsilon = 55$ at 25°C) [47] as reaction medium would cause a greater destabilization of the zwitterionic pentacoordinate intermediate IV. These three arguments point to the same direction; therefore, the reactions of 1 with SA amines in aqueous 44 wt% ethanol should also be concerted (Scheme 2).

Pyridinolysis Reaction

Concerning the pyridinolysis reactions ($\beta = 0.43 \pm$ 0.02, $R^2 = 0.99$), it is noteworthy that the change of SA amines by isobasic pyridines stabilizes the tetrahedral intermediate formed with carbonates [35,36]. If this can be extrapolated to phosphates, it means a stabilization of the pentacoordinate intermediate V relative to IV. Nevertheless, in the case of the pyridinolysis of **1**, in the extreme, the estimated pK_a^0 value could be similar to the pK_a of the most basic pyridine used. This means that for pyridines of pK_a lower than 9.5 the ratedetermining step should be the breakdown to products of the intermediate, and the Brønsted slope should be $\beta = 0.8-1.1$ if the mechanism were stepwise. In contrast, the slope of the Brønsted plot found for 1 is 0.43. Therefore, it is clear that the above discussion rules out a stepwise process for the pyridinolysis of 1, and its mechanism should be concerted. Namely, the stabilization due to the substitution of the SA amino group by a pyridino group in the intermediate would not be sufficient to stabilize intermediate V [35,36].

Taking into account the arguments discussed above and that the product analysis study permits us to disregard the formation of products derived from any aromatic nucleophilic substitution, the most probable mechanism for the pyridinolysis of **1** is shown in Scheme 2.

CONCLUSIONS

- 1. The reactions of diethyl 4-nitrophenyl phosphate triester (1) with phenols, SA amines, and pyridines proceed by concerted mechanisms, with β values in the 0.21–0.43 range.
- 2. The substitution of phenyl by ethoxy in the pentacoordinate intermediate and the change of a given solvent by a less polar one destabilize the intermediate, changing the mechanism from stepwise to concerted.
- 3. The stabilization conferred to the pentacoordinate intermediate by the substitution of an SA amine by a pyridine is not enough to change the mechanism from concerted to stepwise.
- 4. Aromatic substitution in these reactions is ruled out.

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