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Reactivity of the Insecticide Fenitrothion toward O and N Nucleophiles

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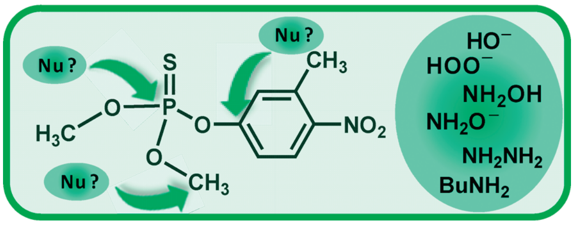

The reactivity of Fenitrothion (**1**) toward several O- and N-based nucleophiles, including ambident and α-nucleophiles, was investigated in basic media at 25 °C in water containing 2% 1,4-dioxane. In the reactions with HO^- and HOO^- quantitative formation of 3-methyl-4-nitrophenoxide (**2**) was observed indicating a $S_N2(P)$ pathway. In the reactions with NH_2OH, NH_2O^-, and $BuNH_2$, demethylfenitrothion (**4**) was formed along with **2**, indicating competition between the $S_N2(P)$ and $S_N2(C)$ pathways; no evidence of a S_NAr pathway was observed in any case. The observed rate constants were dissected into the values corresponding to the $S_N2(P)$ and $S_N2(C)$ pathways. The yield of **4** depends on the nucleophile and on the pH of the reaction, being the main product in the case of $BuNH_2$. With HOO^-, NH_2OH, and NH_2O^- a significant α-effect was observed, confirming the participation of the nucleophile in the rate-limiting step of the reaction.

Introduction

Organophosphorus compounds such as esters and thioesters of phosphoric and thiophosphoric acids are extensively used throughout the world as insecticides and have in many cases replaced organochlorine pesticides.[1] The use of these toxic pesticides has resulted in contamination of soils and groundwater. Natural degradation of organophosphorus pesticides occurs by homogeneous and heterogeneous hydrolysis,[1−3] oxidation,[4] photolysis,[5] and biodegradation,[6] whereas thermic, enzymatic, or photochemical degradation as well as chemical treatments based on the use of strong oxidants or nucleophiles are among the methods used for its destruction.[5,7−10] So, detailed knowledge of the reactivity of these compounds with nucleophiles and oxidants is important for physical organic chemistry as well as for environmental chemistry. We present here our results on the reactivity and regiochemistry of Fenitrothion (**1**) [*O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate] with several O and N nucleophiles including some α-nucleophiles. α-Nucleophiles are nucleophiles which bear nonbonding pairs of electrons at the position α to the nucleophilic center and whose reactivity is greater than would be expected on the basis of the pK_a values.[11] They are of special interest because their high reactivity toward phosphorus makes them reagents of choice for the destruction of nerve gases and other

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organophosphorus poisons.[12] The plough layer of arable soils may contain > 3000 kg N ha^{-1}; most of this is composed of a continuum of complex organic forms. The total soluble N in soils is composed of mineral N and soluble organic N (SON). Studies with fresh soil have indicated that as much SON as mineral N can exist in soil under agricultural cropping systems. In agricultural soils, free amino acids and amino sugars account for < 5% of SON, heterocyclic N bases up to 15%, and amino N in peptides and proteins for 35−57%.[13] So, it is important to study the reactivity of organophosphorus insecticides with N nucleophiles such as amines because the presence of organic N compounds may affect the effectiveness of the insecticides and their fate in soils.

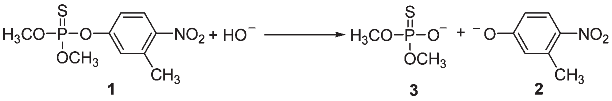
Fenitrothion (**1**) is a broad spectrum insecticide and acaricide used for pest control in rice, vegetables, wheat, cereals, and cotton;[14] it is also considered by the World Health Organization (WHO) effective for the control of the vector of malaria.[15] It has low adult mammalian toxicity but it is a known endocrine disrupting chemical.[16]

Organophosphorus esters and thioesters containing both alkyl and aryl substituents exhibit three reaction pathways for nucleophilic attack: attack at phosphorus, resulting in P−OAr cleavage ($S_N2(P)$); attack at the aliphatic carbon with C−O cleavage ($S_N2(C)$); and attack on the aromatic moiety with Ar−O cleavage (S_NAr).[17−19] These three pathways were detected in the reactions of different nucleophiles with **1**. For instance, the hydrolysis of **1** occurs with C−O cleavage at pH < 8,[20] and with P−OAr cleavage at pH > 9.[3,20−22] Attack on the P center was the only pathway observed for the reaction of **1** with several phenoxides and some O α-nucleophiles,[22] while competition of the S_NAr pathway was found in the reaction with the N nucleophiles *n*-butylamine, ethanolamine, and glycyl ethyl ester.[23] On the other hand, the ethanolysis of **1** with alkali metal alkoxides in anhydrous ethanol proceeds by nucleophilic attack at both P and aliphatic carbon centers and a minor S_NAr route (≤7%) was also detected.[24] The reaction of **1** with a series of α-nucleophile oximates having pK_a values in the range of 7.7−11.8 proceeds through $S_N2(P)$ while in the presence of cetyltrimethylammonium surfactants $S_N2(C)$ was also observed.[25]

In the present work we studied the reactivity and regiochemistry of **1** with HO^-, HOO^-, NH_2OH, NH_2NH_2, and *n*-butylamine ($BuNH_2$) in aqueous basic solutions. Hydrogen peroxide has been used for decontamination of chemical warfare agents,[7] and in advanced oxidation processes for environmental remediation, such as Fenton and photo-Fenton.[26] This oxidant has the advantage over others that it is environmentally friendly leading in some cases to the total mineralization of the organic pollutant.[26a] Hydroxylamine is an ambident α-nucleophile, readily alkylated on nitrogen but often acylated and generally phosphorylated on oxygen, with reaction through oxygen favored for harder electrophiles.[12] In this work, reaction at the P center was the only pathway observed with the two O nucleophiles HO^- and HOO^-, while competition by $S_N2(C)$ was found with the other nucleophiles; no evidence of S_NAr was obtained in any case. An important α-effect was observed with HOO^-, NH_2OH, and NH_2O^-.

Results and Discussion

Hydrolysis Reaction. The hydrolysis of Fenitrothion (**1**) was studied under pseudo-first-order conditions in 2% 1,4-dioxane/H_2O at 25 °C at several NaOH concentrations and at constant ionic strength ($I = 1$ M (NaCl)). The UV−vis spectrum of the product matches that of 3-methyl-4-nitrophenoxide (**2**) at the expected concentration; therefore, as for the reaction studied in 2% acetonitrile (ACN)/H_2O,[21] the only reaction taking place is P−O bond fission, (eq 1), as was previously demonstrated at pH > 8.[20] Further evidence was obtained by following the degradation of a 9.60×10^{-3} M solution of **1** in 1,4-dioxane/D_2O/H_2O (5:47.5:47.5) in the presence of 1.40 M NaOH at room temperature by ^{31}P NMR over a period of 9 days. The initial reading showed a single peak at 65.19 ppm, corresponding to **1**;[24,25] as the reaction proceeded, another peak was observed at 58.13 ppm corresponding to *O*,*O*-dimethylphosphorothioate (**3**);[24,25,27] this was the only peak remaining after all the Fenitrothion was consumed (Figure 1).[28]



(1)

The value of the second-order rate constant for this reaction was calculated from the slope of the linear plot of k_{obs} vs HO^- (Figure S1, Supporting Information) as $(2.50 \pm 0.08) \times 10^{-3}$ M^{-1} s^{-1}. This value is slightly higher than that determined before in 2% ACN/H_2O ($(2.0 \pm 0.1) \times 10^{-3}$ M^{-1} s^{-1}),[21] and is in good agreement with other reported values.[3,20,22]

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[28] The conversion of **1** into products is much slower than predicted by the observed rate constant in dilute solutions. This is due to the fact that under the conditions of the NMR experiments not all the reactant is in solution. Besides, at this high concentration it is likely that the hydrophobic Fenitrothion is aggregated.

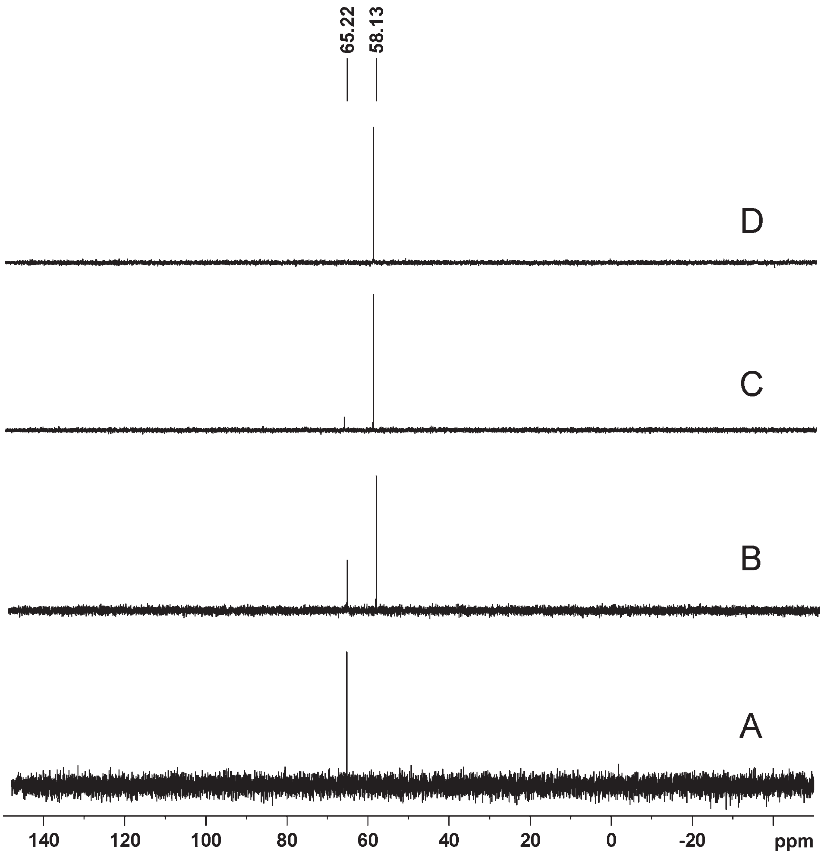
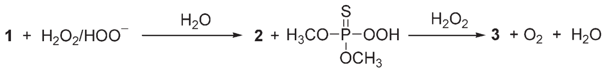


FIGURE 1. ^{31}P NMR spectrum in 1,4-dioxane/D_2O/H_2O (5:47.5:47.5) at room temperature of **1** (9.60×10^{-3} M) in the presence of 1.40 M NaOH at different reaction times: (A) 0, (B) 5, (C) 48, and (D) 213 h.

Reaction with H_2O_2. The reaction of **1** with H_2O_2 was studied in a pH range from 9.00 to 12.40 in 2% 1,4-dioxane/H_2O at 25 °C and I = 1.00 M (NaCl); buffers of H_2O_2 or 0.005 M Borax were used to control the pH of the solutions. The reaction was followed by measuring the appearance of **2** at 397 nm. Quantitative formation of **2** indicates that the only reaction taking place is $S_N2(P)$ as was observed in the hydrolysis reaction. As was previously proposed with other substrates,[27,29,30] we suggest that the reaction taking place is that shown in eq 2. Evolution of bubbles was observed during the kinetic measurements indicating the formation O_2.



$$\mathbf{1} + H_2O_2/HOO^- \xrightarrow{H_2O} \mathbf{2} + H_3CO\text{-}\overset{\overset{\displaystyle S}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}\text{-}OOH \xrightarrow{H_2O_2} \mathbf{3} + O_2 + H_2O \qquad (2)$$

Two sets of experiments were conducted in order to determine values of k_{obs} for this reaction. In one of them we worked at different pH values varying the analytical concentration of H_2O_2 ($[H_2O_2]_0$) at each pH; the results are shown in Table S1 (Supporting Information). Another set of experiments was conducted at constant $[H_2O_2]_0 = 4.76 \times 10^{-3}$ M over a pH range from 9.00 to 12.38 and the results are collected in Table S2 (SI).

The nucleophiles present in the reaction solutions were H_2O, HO^-, H_2O_2, and HOO^-, so the expression for k_{obs} is given by eq 3. The plots of k_{obs} vs $[H_2O_2]_0$ according to eq 3 at each pH are linear (Figure S2, SI) and from the slope of these plots the values of the second-order rate constants ($k_{[H_2O_2]_0}$) at each pH were calculated (Table S3, SI). The intercepts of the plots of Figure S2 (SI) are indistinguishable from zero, within experimental error, indicating that H_2O and HO^- ion do not compete with H_2O_2. The expression for $k_{[H_2O_2]_0}$ is given by eq 6. It can be seen in Table S3 (SI) that the values of $k_{[H_2O_2]_0}$ obtained increase with pH.

$$\begin{aligned} k_{obs} &= k_{H_2O} + k_{HO^-}[HO^-] + k_{H_2O_2}[H_2O_2] + k_{HOO^-}[HOO^-] \\ &= k_{H_2O} + k_{HO^-}[HO^-] + (k_{H_2O_2}X_{H_2O_2} \\ &\quad + k_{HOO^-}X_{HOO^-})[H_2O_2]_0 \end{aligned} \qquad (3)$$

$$X_{H_2O_2} = \frac{[H_2O_2]}{[H_2O_2]_0} \qquad (4)$$

$$X_{HOO^-} = \frac{[HOO^-]}{[H_2O_2]_0} \qquad (5)$$

$$\begin{aligned} k_{[H_2O_2]_0} &= k_{H_2O_2}X_{H_2O_2} + k_{HOO^-}X_{HOO^-} \\ &= k_{H_2O_2} + (k_{HOO^-} - k_{H_2O_2})X_{HOO^-} \end{aligned} \qquad (6)$$

From a plot of $k_{[H_2O_2]_0}$ vs X_{HOO^-} according to eq 6, the second-order rate constant for H_2O_2 and HOO^- can be calculated from the intercept at $X_{HOO^-} = 0$ and 1, respectively (Figure S3, SI). The intercept at $X_{HOO^-} = 0$ is zero,

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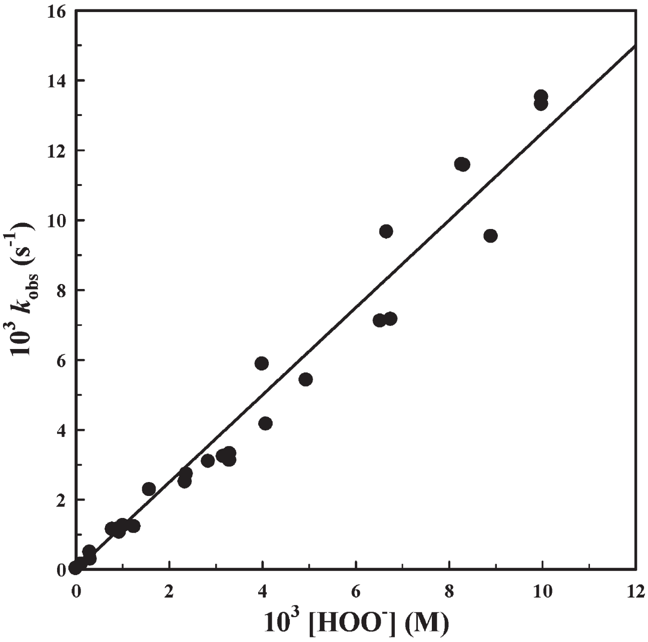

FIGURE 2. Plot of k_{obs} vs [HOO^-] for the reaction of **1** with H_2O_2 at a pH range from 9.00 to 12.38 at 25 °C. Solvent contains 2% 1,4-dioxane; ionic strength $I = 1$ M (NaCl); $[\mathbf{1}]_0 = 4.76 \times 10^{-5}$ to 6.10×10^{-5} M. Data from Tables S1 and S2, SI.

within experimental error; therefore H_2O_2 does not compete as a nucleophile with HOO^-. The value of $k_{HOO^-} = 1.11 \pm 0.07$ M^{-1} s^{-1} was obtained from the intercept at $X_{HOO^-} = 1$.

With the data presented in Table S2 (SI) obtained at constant $[H_2O_2]_0$ and varying the pH we calculated $k_{HOO^-} = 1.08 \pm 0.05$ M^{-1} s^{-1} from the slope of the straight line of $k_{obs}/[H_2O_2]_0$ vs X_{HOO^-} (Figure S4, SI), in good agreement with the value obtained above that corresponds to another set of experiments. By plotting together all the values of k_{obs} obtained in the two series of experiments against [HOO^-] (Figure 2), $k_{HOO^-} = 1.25 \pm 0.03$ M^{-1} s^{-1} was calculated.

As the pK_a of H_2O_2 is 11.6,[22] in the pH range used for this study, both H_2O_2 and HOO^- are present in the reaction solution. The results indicate that only the HOO^- ion acts as a nucleophile toward **1**. Besides, this anion is 500 times more reactive than HO^- in spite of the fact that it is less basic than the latter (p$K_a^{H_2O} = 15.74$);[31] this could be attributed to the fact that HOO^- is an α-nucleophile.

Several studies have previously demonstrated the α-effect in nucleophilic attack at the P center.[11,17,22,27,29,30,32,33] An α-effect of 210 for the HOO^-/ HO^- pair was reported before for the reaction with **1**,[22] this is less than half the value that we calculated and the difference arises from differences in the values of k_{HOO^-} reported there. In spite of the fact that the magnitude of the α-effect is substrate-dependent,[22] we have calculated an α-effect of 465 for the same pair of nucleophiles for the reaction with Chlorpyrifos-methyl.[27]

Reaction with NH_2OH. The reaction of **1** with NH_2OH was studied in 2% 1,4-dioxane/H_2O at 25 °C and $I = 1.00$ M (NaCl) in a pH range from 9.00 to 12.00; buffers of NH_2OH or 0.005 M Borax were used to control the pH of the solutions. In this pH range the predominant form of the nucleophile is neutral NH_2OH (p$K_a^{H_3NOH} = 6.19$, p$K_a^{H_2NOH} = 13.74$).[34] The reaction was followed by measuring the increase in absorbance at 397 nm corresponding to the formation of **2**, the product of attack at the phosphorus center. It was noted that the absorbance at infinite time of the aryloxide product (A_{inf}) was lower than that predicted when the reaction occurred solely via $S_N2(P)$. The amount of **2** formed, calculated from A_{inf}, varied from 62% at pH 9 to 93% at pH 12. Besides, the spectra taken at different reaction times at pH 9.00 are different from those taken at pH 12 (Figure S5, SI).

The deviation of A_{inf} values from the expected value suggested the competition of another reaction pathway: a S_N2 process involving nucleophilic attack at the aliphatic methoxy atom and/or a S_NAr process in which the nucleophile attacks the C-1 position of the aromatic moiety. To fully identify the reaction products, ^{31}P NMR and GC-MS experiments were conducted.

The degradation of a 0.02 M solution of **1** with 0.50 M NH_2OH at pH 10.00 (buffer Borax 0.005 M) in 2% 1,4-dioxane/D_2O at room temperature was followed by ^{31}P NMR over 120 h. The initial reading showed a single peak at 65.14 ppm, corresponding to the chemical shift of **1** (Figure 3). After 6 h of reaction the signal corresponding to **1** decreased while two peaks were observed: one at 58.33 ppm and another at 53.53 ppm. After 120 h no signal corresponding to **1** was observed and only the peaks at 58.33 and 53.53 ppm remained. The signal at 58.33 ppm was attributed to **3** and that at 53.53 ppm to demethylfenitrothion (**4**), by comparison with reported values.[24,25]

By GC-MS analysis of a reaction conducted at a higher concentration of **1** (see the Experimental Section and the Supporting Information) the presence of **2** was detected in the ether extract of the reaction mixture (Figure S6, SI). With the experimental setup employed, the aqueous extract of this reaction showed no signals by GC, but the ^{31}P NMR spectrum showed the presence of **4** (Figure S7, SI). No evidence of a S_NAr pathway was observed.

In Scheme 1 the reactions that lead to the formation of **2**, **3**, and **4** are depicted. The formation of **4** is attributed to the reaction of NH_2OH at the aliphatic C atom by a $S_N2(C)$ pathway. Formation of **3** can occur by two competitive $S_N2(P)$ pathways: hydrolysis of **1** and attack of NH_2OH on P that leads to an *O*-phosphorylated derivative that decomposes in the presence of an excess of hydroxylamine. It was previously proposed that in the reaction of NH_2OH with bis(2,4-dinitrophenyl) phosphate the initial product of attack of the P center by the O of the nucleophile is converted to 2,4-dinitrophenyl phosphate by an excess of NH_2OH liberating N_2 and NH_3.[34] Besides, it was demonstrated that the reaction of NH_2OH with 2,4-dinitrophenyl diethyl phosphate gives initially an *O*-phosphorylated derivative that decomposes in the presence of an excess of NH_2OH.[35]

Values of k_{obs} for the reaction of **1** with NH_2OH were obtained at different pH values as a function of the analytical

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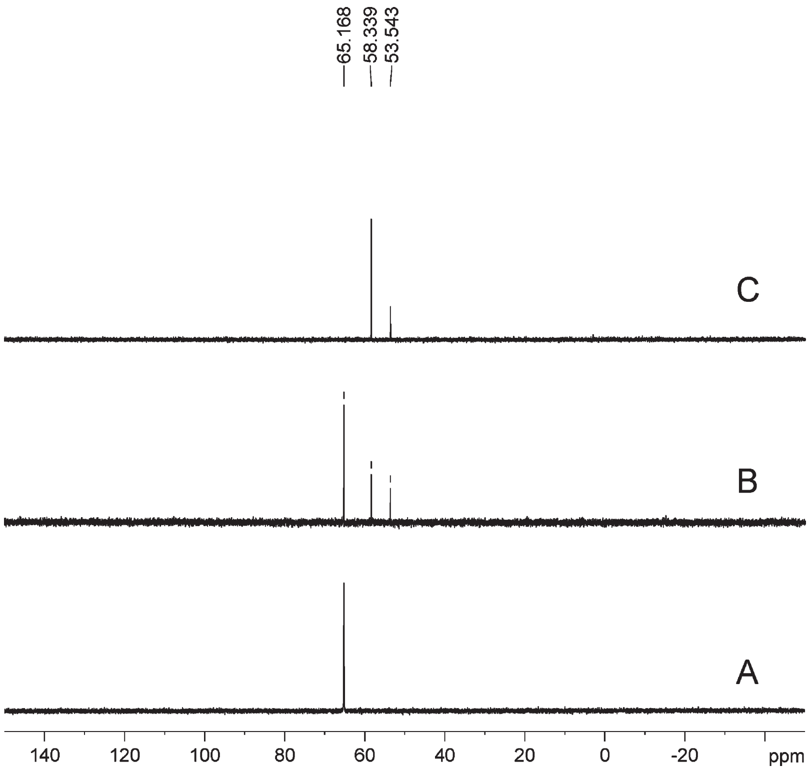
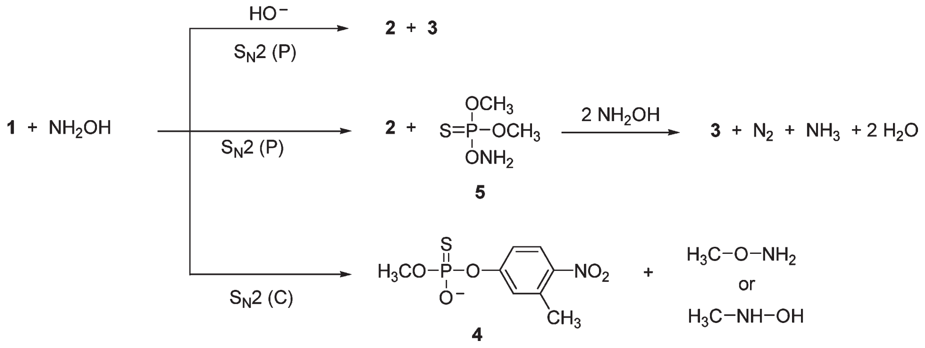


FIGURE 3. ^{31}P NMR spectrum in 2% 1,4-dioxane/D_2O at room temperature of **1** (0.02 M) in the presence of 0.50 M NH_2OH at pH 10.00 at different reaction times: (A) 0, (B) 6, and (C) 120 h.

SCHEME 1. Reaction Pathways for the Reaction of Fenitrothion with NH_2OH



concentration of the nucleophile ($[NH_2OH]_0$) (Table S4, SI). Combining eqs 7 and 8, the observed rate constants for the attack at P (k_{obs}^{P}) and at C (k_{obs}^{C}) can be calculated.

$$k_{obs} = k_{obs}^{P} + k_{obs}^{C} \qquad (7)$$

$$\frac{k_{obs}^{P}}{k_{obs}^{C}} = \frac{[\mathbf{2}]}{[\mathbf{4}]} \qquad (8)$$

The concentration of 3-methyl-4-nitrophenoxide ion (**2**) was determined directly from spectrophotometric measurements, while the concentration of **4** was determined by subtracting $[\mathbf{2}]_{inf}$ from $[\mathbf{1}]_0$.

It can be seen from the data in Table S4 (SI) that at constant pH and variable NH_2OH concentration, the yield of products is constant and that the amount of attack at P increases from 62% to 93% when the pH changes from 9 to 12. By plotting the values of k_{obs}^{P} and k_{obs}^{C} as a function of $[NH_2OH]_0$ at each pH, we calculated from the slope of the linear plots the second-order rate constant for the attack of NH_2OH at P and at the aliphatic C according to eqs 9 and 10 (Figures 4 and 5, respectively, Table S5, SI). In all cases, the intercepts of the plots are indistinguishable from zero, within experimental error, indicating that H_2O and HO^-, the other nucleophiles present in the reaction media, do not compete with NH_2OH. From the second-order rate constant for the hydrolysis reaction, we can calculate that the contribution of HO^- to the attack over P will be $2.5 \times 10^{-8}\ s^{-1}$ at pH 9 and $2.5 \times 10^{-5}\ s^{-1}$ at pH 12. Thus, the term corresponding to the hydrolysis reaction may be neglected in eq 9.

$$\begin{aligned} k_{obs}^{P} &= k_{HO}^{P}[HO^-] + k_{NH_2OH}^{P}[NH_2OH] + k_{NH_2O^-}^{P}[NH_2O^-] \\ &= k_{HO}^{P}[HO^-] + (k_{NH_2OH}^{P}X_{NH_2OH} \\ &\quad + k_{NH_2O^-}^{P}X_{HH_2O^-})[NH_2OH]_0 \end{aligned} \qquad (9)$$

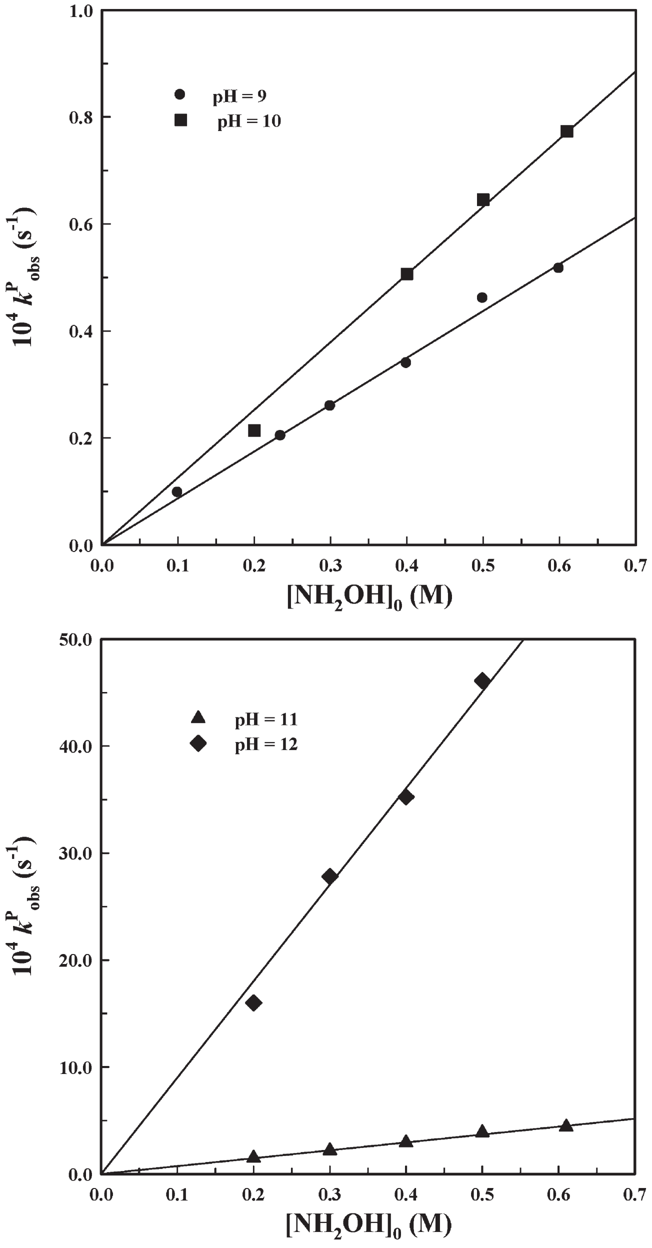


FIGURE 4. Plot of k^P_{obs} vs $[NH_2OH]_0$ for the reaction of Fenitrothion (**1**) with NH_2OH at 25 °C at different pH values. Solvent contains 2% 1,4-dioxane; ionic strength, I = 1 M (NaCl); $[\mathbf{1}]_0 = 5.88 \times 10^{-5}$ to 6.60×10^{-5} M.

$$k^C_{obs} = k^C_{NH_2OH}[NH_2OH] + k^C_{NH_2O^-}[NH_2O^-] = (k^C_{NH_2OH}X_{NH_2OH} + k^C_{NH_2O^-}X_{NH_2O^-})[NH_2OH]_0 \quad (10)$$

$$X_{NH_2OH} = \frac{[NH_2OH]}{[NH_2OH]_0} \quad (11)$$

$$X_{NH_2O^-} = \frac{[NH_2O^-]}{[NH_2OH]_0} \quad (12)$$

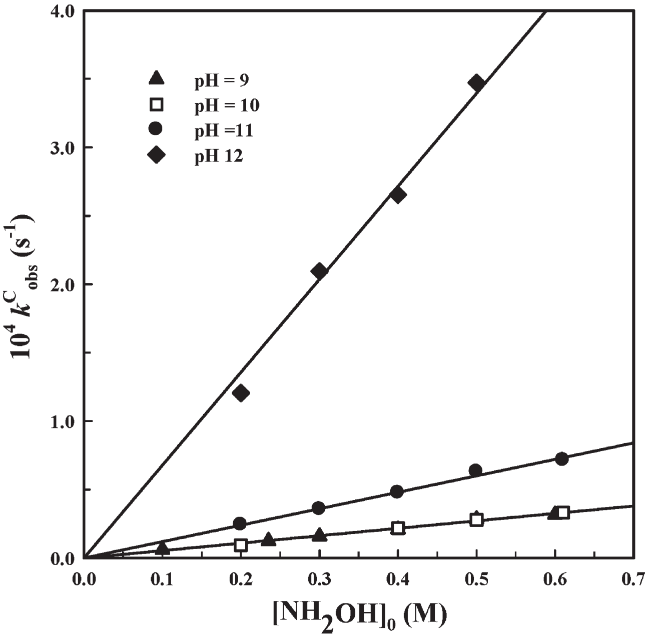


FIGURE 5. Plot of k^C_{obs} vs $[NH_2OH]_0$ for the reaction of Fenitrothion (**1**) with NH_2OH at 25 °C at different pH values. Solvent contains 2% 1,4-dioxane; ionic strength, I = 1 M (NaCl); $[\mathbf{1}]_0 = 5.88 \times 10^{-5}$ to 6.60×10^{-5} M.

TABLE 1. Second-Order Rate Constants for the $S_N2(P)$ and $S_N2(C)$ Pathways for the Reaction of Fenitrothion (1) with NH_2OH at 25 °C[a]

$k^P_{NH_2OH}$ ($M^{-1}\,s^{-1}$)	$(0.88 \pm 0.01) \times 10^{-4}$	$k^P_{NH_2O^-}/k^P_{NH_2OH}$	5682
$k^P_{NH_2O^-}$ ($M^{-1}\,s^{-1}$)	0.500 ± 0.006	$k^C_{NH_2O^-}/k^C_{NH_2OH}$	647
$k^C_{NH_2OH}$ ($M^{-1}\,s^{-1}$)	$(0.536 \pm 0.008) \times 10^{-4}$	$k^P_{NH_2OH}/k^C_{NH_2OH}$	1.6
$k^C_{NH_2O^-}$ ($M^{-1}\,s^{-1}$)	$(3.47 \pm 0.07) \times 10^{-2}$	$k^P_{NH_2O^-}/k^C_{NH_2O^-}$	14.4

[a] Solvent contains 2% 1,4-dioxane; ionic strength, I = 1 M (NaCl); $[\mathbf{1}]_0 = 5.88 \times 10^{-5}$ to 6.60×10^{-5} M.

To calculate the second-order rate constants for the neutral and anionic forms of the nucleophile, plots of $k^P_{[NH_2OH]_0}$ and $k^C_{[NH_2OH]_0}$ vs $X_{NH_2O^-}$ were constructed (Figures S8 and S9, respectively, SI) and the values obtained from the intercept of the plots at $X_{NH_2O^-}$ = 0 and 1 are collected in Table S6 (SI).

The reaction of **1** with NH_2OH was also evaluated from another set of experiments. Several reactions were conducted at different pH values and constant $[NH_2OH]_0$ = 0.40 M and the results are collected in Table S7 (SI). From plots of $k^P_{obs}/[NH_2OH]_0$ and $k^C_{obs}/[NH_2OH]_0$ vs $X_{NH_2O^-}$ (Figures S10 and S11, respectively, SI), values for the second-order rate constants for attack of neutral and anionic nucleophile over P and aliphatic C atom were calculated and the results are shown in Table S6 (SI).

It can be seen in Table S6 (SI) that the values calculated for $k^P_{NH_2O^-}$ and $k^C_{NH_2O^-}$ from the two sets of experiments are in good agreement. So, we calculate $k^P_{NH_2O^-} = 0.500 \pm 0.006\ M^{-1}\,s^{-1}$ and $k^C_{NH_2O^-} = (3.47 \pm 0.07) \times 10^{-2}\ M^{-1}\,s^{-1}$ as the mean value of those reported in Table S6 (SI). On the other hand, the intercept of the plots of Figures S8 and S10 (SI) at $X_{NH_2O^-}$ = 0 that gives the second-order rate constant $k^P_{NH_2OH}$ is zero, within experimental error, although the intercepts at $X_{NH_2O^-}$ = 1 that give the values of $k^C_{NH_2OH}$ are in good agreement. To obtain better values for $k^P_{NH_2OH}$ and $k^C_{NH_2OH}$ we used the experiments conducted at pH 9.00 and variable $[NH_2OH]_0$ (Table S4, SI), because at pH 9.00 $X_{NH_2O^-}$ is negligible (Table S5, SI). In Table 1 are

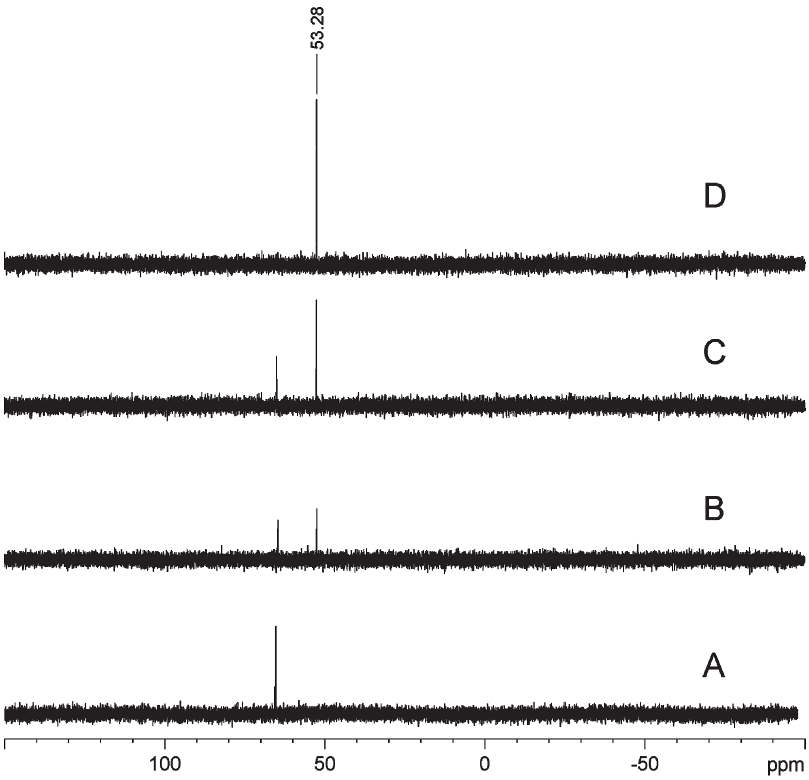


FIGURE 6. ^{31}P NMR spectrum in 1,4-dioxane/D_2O/H_2O (5:9.5:85.5) at room temperature of **1** (3.99×10^{-3} M) in the presence of 0.20 M $BuNH_2$ at pH 10.05 at different reaction times: (A) 15 min, (B) 7 h, (C) 24 h, and (D) 70 h.

collected the values of the second-order rate constants for the neutral and anionic nucleophile reacting by the $S_N2(P)$ and $S_N2(C)$ pathways along with their relative reactivity.

It can be seen from the data in Table 1 that NH_2O^- is more than 5600 times more reactive than NH_2OH for the attack at the phosphorus center, whereas for the reaction at the aliphatic carbon atom, the anion is 600 times more reactive than its neutral form. This difference in reactivity of the anionic and neutral hydroxylamine is much higher than that observed for bis(2,4-dinitrophenyl) phosphate, i.e. 103.[34] Other authors reported ratios of 1900 and 3700 for diethyl 4-nitrophenyl phosphate and ethyl 4-nitrophenyl phosphate, respectively, and 26 000 and 200 000 for 4-nitrophenyl acetate and 4-nitrophenyl dimethylcarbamate, respectively.[36] They have pointed out that hydroxylamine is the only compound that in aqueous solution gives rise to two reactive O-nucleophilic species, NH_2OH and NH_2O^-, whose basicities differ very strongly, only comparable with the difference in the basicities of oxygen in a neutral water molecule and hydroxide ion, and that the differences in the kinetic behavior of NH_2OH and NH_2O^- are also surprising.[36] On the other hand, neutral NH_2OH is almost as reactive toward P as to aliphatic C, whereas NH_2O^- is 14 times more reactive toward P than to aliphatic C. For the anionic nucleophile the reaction with P is predominant.

Reaction with $BuNH_2$. The reaction of **1** with $BuNH_2$ was studied in a pH range from 10.00 to 11.50 in 2% 1,4-dioxane/H_2O at 25 °C and $I = 1.00$ M (NaCl); buffers of $BuNH_2$ were used to control the pH of the solutions. The reaction was followed by measuring the appearance of **2** at 397 nm. As was observed in the reaction with NH_2OH, the absorbance at infinite time at the wavelength maximum of the aryloxide product (A_{inf}) was lower than that predicted if the reaction occurred solely via $S_N2(P)$. The yield of **2** increases with pH and decreases with [$BuNH_2$] at constant pH, varying from 6% at pH 10.00 to 25% at pH 11.50.

To identify the reaction products, the degradation of a 3.99×10^{-3} M solution of **1** with 0.20 M $BuNH_2$ at pH 10.05 in 1,4-dioxane/D_2O/H_2O (5:9.5:85.5) at room temperature was followed by ^{31}P NMR over a period of 70 h. The initial spectrum showed a single peak at 65.28 ppm, corresponding to **1**. After 7 h of reaction another signal was observed at 53.28 ppm corresponding to **4**; this signal increases with reaction time while that of **1** decreases; at 70 h only the signal of **4** is observed (Figure 6). No signal corresponding to **3** was observed; this compound may be formed by hydrolysis of **1** (eq 1) or by S_NAr. Considering that in the reaction with $BuNH_2$ at this pH the yield of **2** is less than 6%, it is not unexpected that there is an absence of the signal corresponding to the formation of **3** or other signal corresponding to a product formed by the attack of $BuNH_2$ at P.

On the other hand, when the degradation of **1** with $BuNH_2$ was followed at pH 11.84 by ^{31}P NMR, the presence of **3** was evidenced after 60 min of reaction (Figure S12, SI).

By analysis of a reaction of **1** at higher concentration with $BuNH_2$ at pH 10.00 (see the SI) the presence of **2** was confirmed by tlc and formation of **4** was evidenced by ^{31}P NMR and UV−vis spectrum. The presence of butylmethylamine, which arises from the attack of $BuNH_2$ at the aliphatic C atom, was detected by ^1H NMR in a reaction conducted with $[\mathbf{1}]_0$ = [$BuNH_2$] free base (Figure S13, SI).

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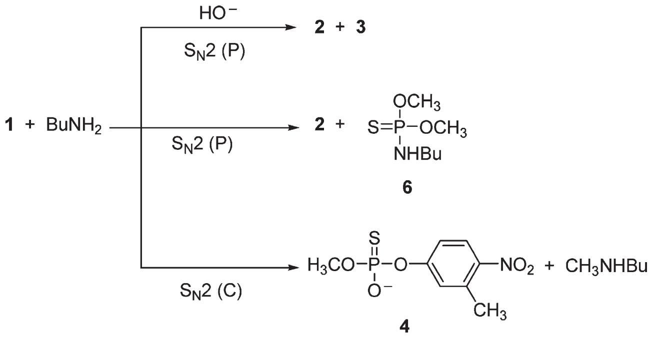
[36] Simanenko, Yu. S.; Popov, A. F.; Prokop'eva, T. M.; Karpichev, E. A.; Savelova, V. A.; Suprun, I. P.; Bunton, C. A. *Russ. J. Org. Chem.* **2002**, *38*, 1286–1298.

SCHEME 2. **Reaction Pathways for the Reaction of Fenitrothion with $BuNH_2$**



The proposed reaction pathways for the reaction of **1** with $BuNH_2$ are shown in Scheme 2 and include $S_N2(P)$ and $S_N2(C)$, as was observed with NH_2OH.

Values of k_{obs} for the reaction of **1** with $BuNH_2$ were obtained at different pH values as a function of the analytical concentration of the nucleophile ($[BuNH_2]_0$) (Table S8, SI). The observed rate constants were dissected into k^P_{obs} and k^C_{obs}, according to eqs 7 and 8. The yield of **2** and **4** was calculated as described before.

The second-order rate constants for the attack of $BuNH_2$ on P and on the aliphatic C atom were calculated from plots of k^P_{obs} and k^C_{obs} vs $[BuNH_2]_0$ according to eqs 13 and 14 (Figures 7 and 8, respectively) and the results are collected in Table S9 in the SI.

$$k^P_{obs} = k^P_{HO}[HO^-] + k^P_{BuNH_2}[BuNH_2]$$

$$= k^P_{HO}[HO^-] + k^P_{BuNH_2} X_{BuNH_2}[BuNH_2]_0 \quad (13)$$

$$k^C_{obs} = k^C_{BuNH_2}[BuNH_2] = k^C_{BuNH_2} X_{BuNH_2}[BuNH_2]_0 \quad (14)$$

$$X_{BuNH_2} = \frac{[BuNH_2]}{[BuNH_2]_0} \quad (15)$$

By plotting the intercepts of plots in Figure 7 as a function of $[HO^-]$ (Figure S14, SI) we obtained from its slope a value of $(2.7 \pm 0.1) \times 10^{-3}$ M^{-1} s^{-1} for the second-order rate constant for the hydrolysis reaction, in very good agreement with that calculated in the absence of $BuNH_2$ (see above). To calculate the second-order rate constants for the reaction of the $BuNH_2$ free base with P and aliphatic C atom, we plotted $k^P_{[BuNH_2]_0}$ and $k^C_{[BuNH_2]_0}$ vs X_{BuNH_2} according to eqs 16 and 17 (Figures S15 and S16, respectively, in the SI). From the intercepts of these plots at $X_{BuNH_2} = 1$, the values of $k^P_{BuNH_2} = (1.13 \pm 0.08) \times 10^{-5}$ M^{-1} s^{-1} and $k^C_{BuNH_2} = (3.16 \pm 0.07) \times 10^{-4}$ M^{-1} s^{-1} were calculated. The ratio $k^P_{BuNH_2}/k^C_{BuNH_2} = 0.0358$ is 45 times smaller than that obtained for NH_2OH (see Table 1) suggesting that NH_2OH is reacting by the oxygen.

$$k^P_{[BuNH_2]_0} = k^P_{BuNH_2} X_{BuNH_2} \quad (16)$$

$$k^C_{[BuNH_2]_0} = k^C_{BuNH_2} X_{BuNH_2} \quad (17)$$

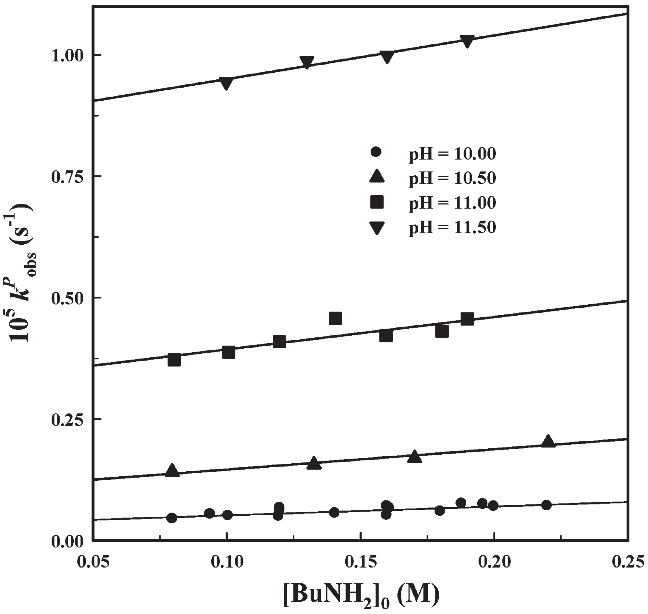


FIGURE 7. Plot of k^P_{obs} vs $[BuNH_2]_0$ for the reaction of Fenitrothion (**1**) with $BuNH_2$ at 25 °C at different pH values. Solvent contains 2% 1,4-dioxane; ionic strength, I = 1 M (NaCl); $[1]_0 = 4.80 \times 10^{-5}$ to 5.50×10^{-5} M.

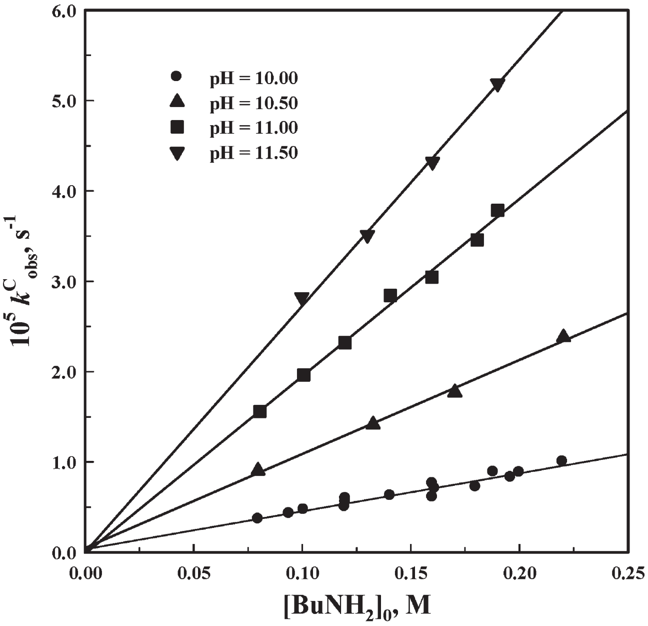


FIGURE 8. Plot of k^C_{obs} vs $[BuNH_2]_0$ for the reaction of Fenitrothion (**1**) with $BuNH_2$ at 25 °C at different pH values. Solvent contains 2% 1,4-dioxane; ionic strength, I = 1 M (NaCl); $[1]_0 = 4.80 \times 10^{-5}$ to 5.50×10^{-5} M.

Reaction with NH_2NH_2. The reaction of **1** with NH_2NH_2 was studied at pH 9.00 (Buffer: Borax 0.005 M) and 12.00 (Buffer: NaOH) with $[NH_2NH_2]_0$ 0.05 and 0.20 M in 2% 1,4-dioxane/H_2O at 25 °C and I = 1.00 M (NaCl). The reaction was followed by measuring the appearance of **2** at 397 nm. In all the reactions the infinity absorbance was less than that calculated for total conversion to **2**. To identify the reaction products, the reaction of **1** with NH_2NH_2 under pseudo-first-order conditions at pH 9.015 was followed by ^{31}P NMR (Figure S17, SI). At the end of the reaction in the ^{31}P NMR spectrum was observed only one signal at 53.38 ppm corresponding to product **4**; no signal corresponding to

TABLE 2. Kinetic Parameters for the $S_N2(P)$ and $S_N2(C)$ Pathways for the Reaction of Fenitrothion (1) with Different Nucleophiles

		$S_N2(P)$		$S_N2(C)$	
nucleophile	pK_a	k^P (M^{-1} s^{-1})	k^P relative	k^C (M^{-1} s^{-1})	k^C relative
HO^-	15.74	$(2.50 \pm 0.08) \times 10^{-3}$	1	N.R.[a]	
NH_2O^-	13.74	0.504 ± 0.009	201.6	$(3.52 \pm 0.03) \times 10^{-2}$	1
HOO^-	11.60	1.25 ± 0.05	500	N.R.[a]	
$BuNH_2$	10.84	$(1.13 \pm 0.08) \times 10^{-5}$	0.00452	$(3.16 \pm 0.07) \times 10^{-4}$	0.00898
NH_2OH	6.19	$(0.88 \pm 0.01) \times 10^{-4}$	0.0352	$(5.36 \pm 0.08) \times 10^{-5}$	0.00152
H_2O[b]	−1.54	1.24×10^{-9}		4.83×10^{-10}	

[a] N.R. = no reaction. [b] Calculated from ref 20.

product **3** was observed, probably due to low concentration. So, as observed with the other N^- based nucleophiles, competition between $S_N2(P)$ and $S_N2(C)$ pathways occurs in this reaction.

In the reactions followed by UV−vis spectrophotometry, decomposition of **2** was detected. When the UV−vis spectra of a solution of **2** (4.71×10^{-5} M) in the presence of 0.20 M NH_2NH_2 at pH 9.00 and 12.00 were recorded at different times, a decrease in the absorbance at 397 nm was observed. At pH 12.00 the observed rate constant for the decomposition of **2** was calculated as $(4.2 \pm 0.3) \times 10^{-6}$ s^{-1}. No attempts to identify the product were made.

By fitting the absorbance vs time data of the reaction of **1** with NH_2NH_2 at pH 12.00 to a biexponential equation, two rate constants were calculated as $k_1 = (7.9 \pm 0.5) \times 10^{-5}$ s^{-1} and $k_2 = (4.4 \pm 0.7) \times 10^{-6}$ s^{-1} (Figure S18, SI); k_2 is attributed to the decomposition of **2** because it is the same, within experimental error, as that determined from a solution of **2** at the same pH. From standard methods[37] we calculated the time at which the maximum value of absorbance at 397 nm will be reached and the concentration of **2** at that time; so, we can estimate the yield of **2** as 38%. The observed rate constant for the consumption of **1**, k_1, can be dissected into k^P_{obs} and k^C_{obs} from which we calculated $k^P_{NH_2NH_2} = 1.51 \times 10^{-4}$ M^{-1} s^{-1} and $k^C_{NH_2NH_2} = 2.47 \times 10^{-4}$ M^{-1} s^{-1}.

Reactivity and Regioselectivity of the Reaction of Fenitrothion with Nucleophiles. The results presented here on the reaction of Fenitrothion in aqueous basic media with several O- and N-based nucleophiles indicate that **1** reacts only by a $S_N2(P)$ pathway with the O nucleophiles HO^- and HOO^-, as was previously reported.[3,20−22] In the reactions with the other nucleophiles, NH_2OH, NH_2O^-, $BuNH_2$, and NH_2NH_2, competition between $S_N2(P)$ and $S_N2(C)$ pathways was observed. No evidence of a S_NAr pathway was obtained in any case.

The behavior of the hard O nucleophiles HO^- and HOO^- can be explained by the HSAB theory,[38] in which case the "hard" oxygen nucleophiles react mainly with the "hard" P electrophilic center. In the case of the N-based nucleophile $BuNH_2$, the same theory can explain the favored reaction of this "soft" nucleophile with the "soft" electrophile, the aliphatic carbon atom.

In the case of the highly reactive α-nucleophile NH_2O^-, the main pathway is $S_N2(P)$ although competition between $S_N2(P)$ and $S_N2(C)$ is observed, whereas NH_2OH is almost as reactive toward P as toward the aliphatic C center.

The absence of evidence of a S_NAr pathway could be explained by the fact that in **1** there is only one electron-withdrawing nitro group on the aromatic ring, so it is unlikely to be sufficiently electron deficient to favor a S_NAr reaction.[39] Consequently, little participation of this pathway, if any, would be expected.

In Table 2 are summarized the second-order rate constants for the $S_N2(P)$ and $S_N2(C)$ pathways of the reaction of **1** with all the nucleophiles studied. The reactivity decreases in the order $HOO^- > NH_2O^- > HO^- > NH_2OH > BuNH_2$ for the reaction on the P center, whereas for the reaction on the aliphatic C it decreases in the order $NH_2O^- > BuNH_2 > NH_2OH \gg HOO^-, HO^-$. The most reactive nucleophile and the one with the largest α-effect is the peroxide anion HOO^-, which is 2.46 times more reactive than the anion of hydroxylamine NH_2O^- although the latter is over 2 orders of magnitude more basic.

With the data in Table 2 for the $S_N2(P)$ pathway, we have constructed the Brönsted-type plot shown in Figure 9. The points for the different nucleophiles fall clearly in two lines: one line is defined by the α-nucleophiles HOO^-, NH_2O^-, and NH_2OH and the other by HO^-, $BuNH_2$, and H_2O. From the slope (least-squares) of the line drawn through the points for the α-nucleophiles a value for β_{nuc} of 0.55 was calculated, whereas for the other nucleophiles a value for β_{nuc} of 0.356 was obtained. These values can be compared with that reported before for the reaction of the same substrate with a series of structurally related phenoxides, namely 0.49; in that case the point corresponding to HO^- falls bellow the line defined by the phenoxides and was interpreted as a different solvation of the nucleophiles.[22] Values of β_{nuc} of 0.30 and 0.61 were reported for the reaction of *O*,*O*-dimethyl-2,4-dinitrophenyl phosphate with oxyanion or pyridine nucleophiles, respectively; for the reaction of *O*-methyl-2,4-dinitrophenyl phosphate a value of β_{nuc} of 0.30 was informed for both types of nucleophiles, whereas for α-nucleophiles $\beta_{nuc} = 0.41$ was obtained.[33] A value of $\beta_{nuc} = 0.3$ for the reaction of bis(2,4-dinitrophenyl) phosphate with α-nucleophiles was also reported.[30]

The fact that the point for NH_2OH falls in the line defined by the other α-nucleophiles may indicate that all of them are reacting through oxygen, as was proposed before for the reaction of 2,4-dinitrophenyl ethyl phosphate diester.[33] The same authors proposed that ammonia oxide tautomer $NH_3^+{-}O^-$ is probably the active nucleophile in the reaction of neutral NH_2OH with phosphate triesters.[12,35] The fact that mono- and dimethylation of NH_2OH on nitrogen does not significantly affect rates of initial attack of NHMeOH

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(37) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill, Inc.: New York, 1995; Chapter 4.

(38) Ruff, F.; Csizmadia, I. G. *Organic Reactions. Equilibria, Kinetics and Mechanism*; Elsevier Science: Amsterdam, The Netherlands, 1994; Chapter 10.

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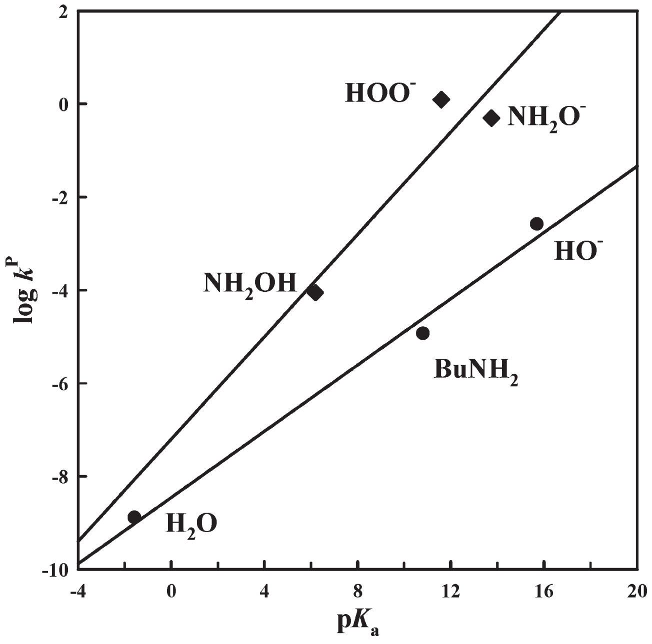

FIGURE 9. Plot of log k_{Nu}^{P} vs pK_a of the nucleophile for the reaction of Fenitrothion (**1**) with different nucleophiles in 2% 1,4-dioxane/H_2O at 25 °C.

and NMe_2OH on bis(2,4-dinitrophenyl) phosphate while *O*-methylation blocks this reaction indicates that neutral NH_2OH can be phosphorylated through oxygen.[34,40] These considerations along with the difference in k_{Nu}^{P}/k_{Nu}^{C} ratios for $BuNH_2$ and NH_2OH found in this study (see above) lead us to believe that NH_2OH is reacting with **1** through the oxygen.

Conclusions

Fenitrothion (**1**) reacts with O- and N-based nucleophiles through different reaction pathways. With the hard nucleophiles HO^- and HOO^- the reaction occurs only by a $S_N2(P)$ pathway, whereas competition between $S_N2(P)$ and $S_N2(C)$ pathways was observed with NH_2OH, NH_2O^-, $BuNH_2$, and NH_2NH_2. With $BuNH_2$, $S_N2(C)$ is the mayor pathway. No evidence of S_NAr was found in any case.

An important α-effect was observed, indicating the participation of the nucleophile in the rate-limiting step of the bimolecular reaction.

The α-nucleophile HOO^- is the most reactive nucleophile of the series studied and is a good candidate for destroying Fenitrothion since $t_{1/2}$ in the presence of 1 M HOO^- is 0.55 s.

Experimental Section

Materials. Fenitrothion was isolated from a commercial sample as described before.[21] A commercial sample of 3-methyl-4-nitrophenol characterized by ^1H NMR, GS-MS, and melting point was used as reference.

Aqueous solutions were prepared with water purified with a Millipore Milli-Q apparatus. $BuNH_2$[41] and 1,4-dioxane[42] were purified as described previously. All of the inorganic reagents were of analytical-reagent grade and were used without further purification. Hydrogen peroxide solutions were titrated with $KMnO_4$ solution standardized by sodium oxalate. NH_2OH solutions were prepared from a commercial aqueous 50% solution potentiometrically titrated in duplicate with HCl. NH_2NH_2 solutions were prepared from a commercial sample and were potentiometrically titrated in duplicate with HCl.

UV−vis spectra were recorded on a double beam or a diode array spectrophotometer and the change in absorbance during a kinetic run was measured on the same instruments.

Kinetic Procedures. Reactions were initiated by adding the substrate dissolved in 1,4-dioxane to a solution containing all the other constituents. The reaction temperature was 25.0 ± 0.1 °C, the ionic strength was 1.0 M and NaCl was used throughout as compensating electrolyte. The solvent contained 2% 1,4-dioxane. In the reactions with H_2O_2, NH_2OH, and NH_2NH_2, water and 1,4-dioxane were degassed and the stock solution of NaCl was filtered by nylon membranes before the reaction solutions were prepared. After the pH was adjusted to the desired value, the solution was sonicated for 5 min and thermostated to 25 °C before the substrate was added.

All kinetic runs were carried out protected from light, under pseudo-first-order conditions, with substrate concentrations of 4.76×10^{-5} to 6.60×10^{-5} M. The reactions were followed by measuring the increase in absorbance of the reaction mixture at 397 nm, the λ_{max} of **2** ($\varepsilon = 17\,641$ cm^{-1} M^{-1}).

Product Analysis Experiments. Two types of product analysis experiments were performed. The first method involved the use of ^{31}P NMR, in a pseudo-first-order experiment. The ^{31}P NMR spectra were recorded on a spectrometer operating at 161.97 MHz. Chemical shifts were measured with respect to the external standard of 85% H_3PO_4 in D_2O/H_2O (75:25). Spectra were acquired with a longitudinal relaxation time (D1) of 3 s with 128 accumulations and proton decoupling. For sample preparation details see the Supporting Information.

The second method of product analysis consists of isolating the products from reactions conducted with initial concentrations of **1** $> 7 \times 10^{-3}$ M and identifying them by standard methods. For details see the Supporting Information.

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Supporting Information Available: Tables and plots of the dependence of the observed rate constants on nucleophile concentration and on pH, tables and plots of the dependence of second-order rate constants on pH and on the free base molar fraction, relevant spectra (UV−vis, ^1H and ^{31}P NMR) for some compounds, and experimental details on product analysis experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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