Determination of the Mechanism of Nucleophilic Reaction of Fenitrothion Using Substituted Phenoxide Nucleophiles in Aqueous Media

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

The mechanism of the nucleophilic displacement reaction at the phosphorus centre of organophosphates was determined. Phenoxide nucleophiles were reacted with fenitrothion (O,O-dimethyl O-(3-methyl-4-nitrophenyl) phosphorothioate) in water at $25^{\circ}C$ and pseudo-first order rate constant measurements taken. Second-order rate constant (k_{Nuc}) was determined for the different concentrations of nucleophiles while the second-order rate constant (k_{lg}) for the investigation of 2,4-dichlorophenoxide ion with and series of aryl phosphorothioate esters was also determined. Linear free energy relationship was further determined using the Brønsted-type plot. The plots are linear over a range of pKa_{Nuc} of 7.15-11.10 that straddles the pKa of the leaving 3-methyl-4-nitrophenoxide ion (pKa = 7.20) with statistically acceptable linear correlations $\log k_{Nuc} = (0.403 \pm 0.01)pKa - 5.971 \pm 0.08(R^2 = 0.987)$ and $\log k_{lg} = (-0.331 \pm 0.03)pKa - 0.477 \pm 0.07(R^2 = 0.980)$. The linearity in the traditional Brønsted-type plots shows the sensitivity of the nucleophilic displacement to the basicity of the nucleophiles and hence is consistent with a single transition-state mechanism whose barrier to decomposition is low hence concerted. Analysis of the values of β_{Nuc}, β_{Lg} and β_{eq} (0.734) with the effective charge distribution in the transition state shows that it has no positive character. The Leffler index presents bond formation being slightly ahead of bond rupture.

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1. INTRODUCTION

The wide application of organophosphorus compounds has ignited serious interest in their reactions and mechanisms of their reactions. The reactions of organophosphorus esters with nucleophiles which are basically phosphoryl transfer are currently a subject of intense study. These processes just like reactions in biological systems are enzyme catalyzed [1] and like all reactions that undergo catalysis by enzymes, reactions of organophosphorus esters undergo tremendous rate enhancements despite the slow reactivity of the compounds and their reacting substrates in the absence of enzymes. The rate enhancement have given rise to controversies that enzyme uncatalysed phosphoryl transfer reactions might proceed by altered mechanisms or another transition states apart from those of the catalyzed reactions. This fact has erupted interest in the enzyme induced mechanisms and is the basis for an intensive contention as to whether the reaction mechanisms for enzyme-catalysed hydrolysis of phosphate esters differ from those of uncatalysed reactions [2]. Bunnett [3] highlighted some factors that could contribute to nucleophilic reactivity for which he found a sound theoretical and experimental precedent. These factors which include geometrical factors (steric hindrance), salvation, ion aggregation, thermodynamic affinity, capacity of Z in :Z - C - X to facilitate expulsion of a leaving group, X etc. have been investigated with regards to Bunnett's review, however more investigation is still needed in some of these factors like solvation. Jencks et al. [4] and Williams et al. [5] investigated the pyridinolysis of phosphoryl pyridinium compounds and concluded that the most likely pathway is a concerted mode with what they called "exploded" transition state having weak bonds attaching the attacking and departing leaving group. Guha et al. [6] worked on the aminolysis of substituted phenyl chlorophosphate with anilines in acetonitrile and reported that the mechanism is concerted with late product like transition state in which bond making and leaving group departure are pronounced.

This work aims at determining the mechanism of nucleophilic displacement on O,O-dimethyl-O-(3-methyl-4-nitrophenyl) phosphorothioate by selected nucleophiles in aqueous media. The linear free energy relationship methodology was used for investigating the reaction mechanism.

2. MATERIALS AND METHODS

A thermostatic water bath of model Genlab WBH6/FL was used to maintain temperature during the kinetic runs. All reactions for kinetic measurements were followed spectrophotometrically, with a UV-Visible spectrophotometer of model 752 using 1cm quartz cuvettes. The pH of solutions before and and after kinetic runs was measured with a PHS-3C pH meter. All reagents and solvents were commercial products used without further purification. While Fenitrothion (*O,O*-Dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate) and 1,4-Dioxane were purchased from Sigma-Aldrich, the nucleophiles which include phenol (PhOH), 4-chloro-3-methylphenol(4-Cl, 3-MePhOH), 3,5-dimethylphenol (3,5-Me$_2$PhOH), 4-Nitrophenol (4-NO$_2$PhOH) and 2-Nitrophenol (2-NO$_2$PhOH), Sodium Chloride (NaCl), Sodium hydroxide (NaOH), distilled water and ethanol (CH$_3$CH$_2$OH) were sourced locally.

2.1 Preparation of Substrate and Nucleophile Stock Solutions

9.0×10^{-4}M of fenitrothion was prepared by adding 2μL of the pure oily liquid into a 10mL volumetric flask and making up to the mark. All nucleophile stock solutions were prepared as follows: a calculated amount of the appropriate compound was weighed into a 25 mL volumetic flask and nucleophile solutions were self-buffered by neutralizing the conjugate acids of the nucleophiles with a molar equivalent of NaOH in the volume base to the nucleophile ratio of 1:2.
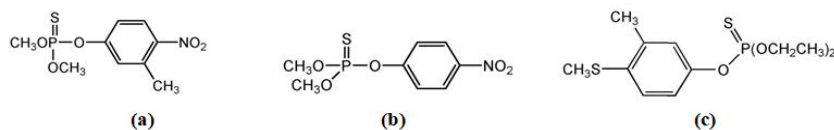

Fig. 1. Fenitrothion, Methyl parathion and Fenthion

2.2 Kinetic Studies

The kinetic measurements used in this work were followed by the procedures described by Omakor et al. [7]. Nucleophile concentrations in the range $1.0×10^{-2}$ to $2.5×10^{-2}$ M were injected into UV cuvettes. A calculated amount of NaCl was added to maintain a constant ionic strength of 1 M. These were equilibrated thermally at $25^{o}C$ for 30min. Reaction was initiated by injecting 20µl of the stock solution of 9.54×10^{-3} M of fenitrothion to the aforementioned cuvettes. The nucleophiles were in sufficient excess of the substrate in order to maintain pseudo-first order kinetics. Initial repetitive scans of the reaction mixture were carried out prior to the kinetic determination to ascertain the appropriate wavelength for monitoring the appearance of product. Infinite absorbance $A_∞$ was obtained when the reading became constant. The pseudo first order rate constant k_{ob} was obtained by regression analysis of the slope of the plot of $ln(A_∞ - A_t)$ vs time. Second order rate constants were obtained from the slope of the plot of k_{ob} vs the various nucleophile concentrations [Nu]. Good linearity with R^2 values ranging between 0.940 and 0.989 was obtained in all cases.

To monitor the effect of leaving group, the substrates were varied fenitrothion (*O,O-*Dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate), methyl parathion (*O,O-*Dimethyl *O*-(4-nitrophenyl) phosphorothioate) and fenthion (*O,O-*Dimethyl *O*-[3-methyl-4-(methylsulfanyl)phenyl] phosphorothioate) , while keeping the nucleophile constant.

3. RESULTS AND DISCUSSION

The second order rate constants, $k_{[Nuc]}(M^{-1}s^{-1})$ for the reaction of fenitrothion with some selected nucleophiles are shown in Table 1. The traditional Brønsted-type plot of $logk_{[Nuc]}$ vs pKa was constructed as shown in Fig. 2. The plot was linear for the nucleophiles used. The solid line defined by the nucleophiles is given by the equation (1):

$$logk_{Nuc} = (0.403 \pm 0.01)pKa - 5.971 \pm 0.08 \quad (1)$$

From which $β_{Nu}$ of $0.40 \pm 0.01(R^2= 0.987)$ was obtained. This value can be compared with $β_{Nu}$ of 0.49 and 0.46 obtained from the reaction of phenoxides with 3-methyl-4-nitrophenyl thiophosphate $(RO)_2$–P(S)–OPhRX [7] and 4-nitrophenyl diphenyl phosphinate $Ph_2P(O)$ – OPhX [8] respectively in aqueous solutions. The latter have been manifestly shown to proceed through concerted mechanism.

Table 1. Tabulation of second order rate constants, k_{nuc} ($M^{-1}s^{-1}$) for the reaction of fenitrothion with some selected nucleophiles measured in water at $25^{o}C$

Nucleophile	pKa	k_{nuc}–$(M^{-1}s^{-1})$ in H_2O	Log k_{nuc}–
PhO⁻	9.95	$1.00 \pm 0.03 \times 10^{-2}$	-1.9986
2-NO₂PhO⁻	7.25	$0.75 \pm 0.09 \times 10^{-3}$	-3.1264
4-NO₂PhO⁻	7.16	$0.83 \pm 0.07 \times 10^{-3}$	-3.0798
2,4-Cl₂PhO⁻	7.19	$1.01 \pm 0.05 \times 10^{-3}$	-2.9973
4-Cl-3-MePhO⁻	9.95	$0.87 \pm 0.02 \times 10^{-2}$	-2.0624

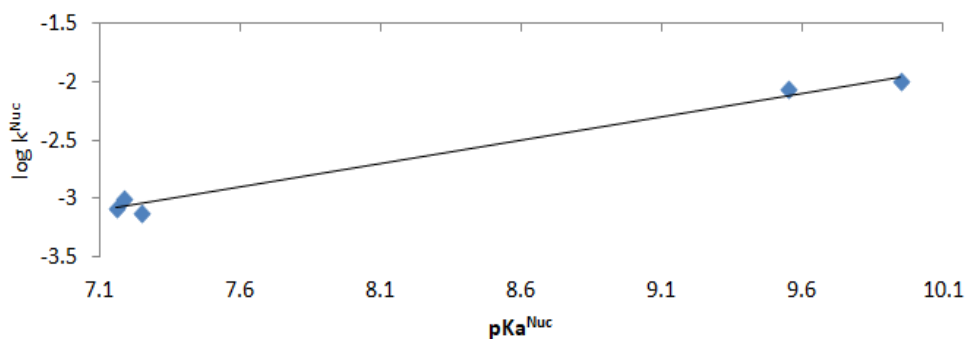*Brønsted coeff. $β_{Nu}$ 0.403 ± 0.01; Corr. coeff. R^2 0.987*

Fig. 2. Brønsted-type plot for the reaction of fenitrothion with substituted phenoxides in water at $25^{o}C$, yielding $β_{Nuc}$–= 0.403 ± 0.01 (r = 0.987)

The kinetic data obtained from the leaving group effect are shown in Table 2. The plot of log k_{lg} vs pKa (Fig 3) which yielded the β_{lg} of -0.331 (R^2 = 0.980) is defined by equation (2)

$$logk_{lg} = (-0.331 \pm 0.03)pKa - 0.477 \pm 0.07 \quad (2)$$

β_{lg} of -0.331 compares well with -0.39, -0.79, 0.87, 0.51, 0.64 obtained for the reaction of PhO⁻ with $(PhO)_2 P(S) - OPh(R)X$ [7], $(EtO)_2P(O) - OPhX$ [9] and $MeO(OH) P(O) - OPhX$ [9] respectively. These reactions have been clearly shown to proceed via concerted mechanism. The value of – 0.33 compares with – 0.30 and – 0.39 obtained foe the hydrolysis of $Me_2P(S) - OPhX$ (Istomin and Eliseeva, 1981) and $(PhO)_2 P(S) - OPh(R)X$ [7] in water at 25^0C. It is observed from the β_{lg} values that the P=S substrates show less degree of bond dissociation in the TS of the reaction with the PhO⁻ than the P=O substrates [9]. The difference may be attributed to the influence of P=O, P=S bonds on the overall reaction rate. It has been reported that the reactions at P=O centres are two to three times faster in magnitude than those at P=S centres – [7]. It has also been suggested that due to the high electronegativity of O compared to S, the phosphorous atom in the phosphoric ester analogues will have more positive character, thus lowering the activation energy and the resultant effect is a higher nucleophilic reactivity.

3.1 Transition State Structure

The linear Brønsted plot shows that the reaction of fenitrothion with phenoxides proceeded through concerted mechanism $[S_N2]$. Furthermore, the effective charge on the entering and leaving oxygen atoms in the transition state can be determined by the use of the $\beta_{Nu,}$ β_{lg} and β_{eq} with β_{eq} being the overall change in charge on the nucleophile or leaving group for the reaction [8,10]. β_{eq} is given by the expression:

$$\beta_{eq} = \beta_{Nu} - \beta_{lg} \quad (3)$$

Hence, $\quad \beta_{eq} = (+0.403) - (-0.331) = 0.734$

Table 2. Kinetic data for polar substituent effect studies in the nucleophilic substitution of fenitrothion in water at 25^oc

Substrate	Leaving group	pKa	k_{lg} (M⁻¹s⁻¹) in H_20	Logk_{lg}
O,O-Dimethyl O-(3-methyl-4-nitrophenyl) phosphorothioate	3-CH₃,4-NO₂-PhO⁻	7.38	$1.01 \pm 0.05 \times 10^{-3}$	-2.9973
O,O-Dimethyl O-(4-nitrophenyl) phosphorothioate	4-NO₂-PhO⁻	7.16	$1.65 \pm 0.07 \times 10^{-3}$	-2.7834
O,O-Dimethyl O-[3-methyl-4-(methylsulfanyl)phenyl] phosphorothioate	3-CH₃,4-SCH₃-PhO⁻	9.9	$1.77 \pm 0.02 \times 10^{-4}$	-3.7532

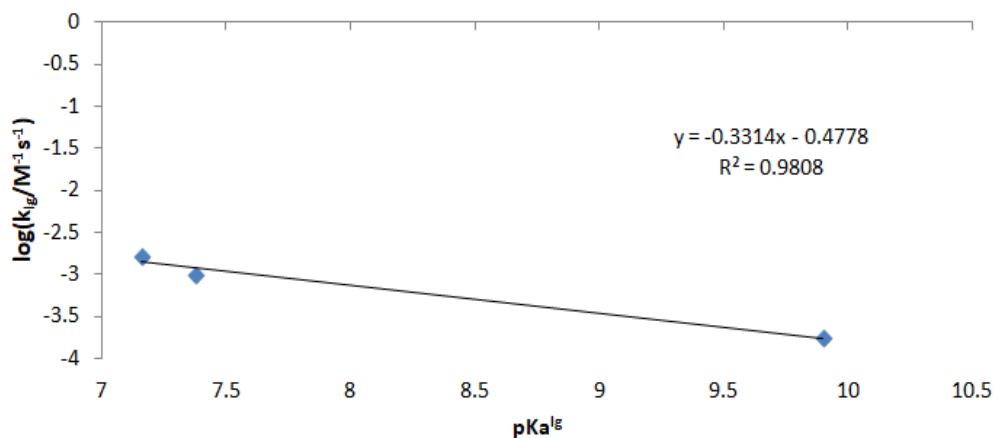*Second-order rate constant, k_{nuc} -0.331 ± 0.03 M⁻¹s⁻¹; Corr. coeff. $R^2$0.980*

Fig. 3. Bronsted-type plot of logk_{lg} vs pKa (leaving group) for the reaction of 2,4-Cl₂PhO⁻ with 1a-c in water at 25^oc

The value of +0.734 is less than+1 charge on a proton. It implies that polar substituent on the equilibrium constant is small for the addition of a thionephosphoryl group than the addition of a proton. That is the dimethyl phosorothioate group is less electron withdrawing than hydrogen. The effective charges on the O of the attacking nucleophile and O of the departing leaving group in moving from the ground state GS to transition state TS $\Delta\varepsilon$(GS→TS) are equal to β_{Nu} (0.403) and β_{lg} (-0.331) respectively. This leaves a charge imbalance of +0.07, which is possibly balanced by -0.07 charge unit on the thiophosphoryl grpoup, so that overall charge neutrality is maintained.

Omakor et al. [7] has reported that the reaction of aryl dimethylphosphorothioate ester with phenoxide nucleophiles in aqueous medium at 25°C afforded an overall change in charge (β_{eq}) of 0.88. Kalu et al. [11] in their reaction of aryl dimethylphosphinothioate esters with anionic oxygen nucleophiles in 70:30 v/v water/ethanol solvent system reported β_{eq} of 1.06 while Williams [5] reported the value of 0.82.The effective charge on the nucleophile in the transition state is given as:

$$\varepsilon_{TS} = \beta_{Nu} + \varepsilon_R$$

where ε_R is the ground state charge on the nucleophile and is given as -1. ε_{TS} Therefore equals -0.60

The Leffler index [5] α, gives the measure of the degree of bonding in the TS for any particular bond. The degree of bond formation, $\propto_{(bf)} = \frac{\beta_{Nu}}{\beta_{eq}}$
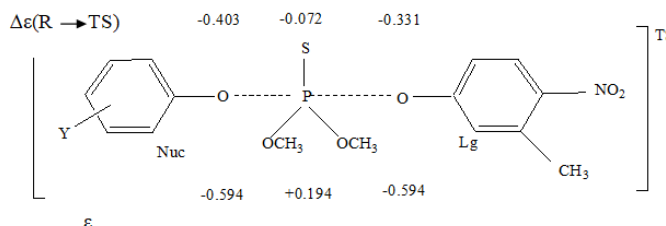
Scheme 1. Representation of the charge distribution in the transition state for the symmetrical reaction in water
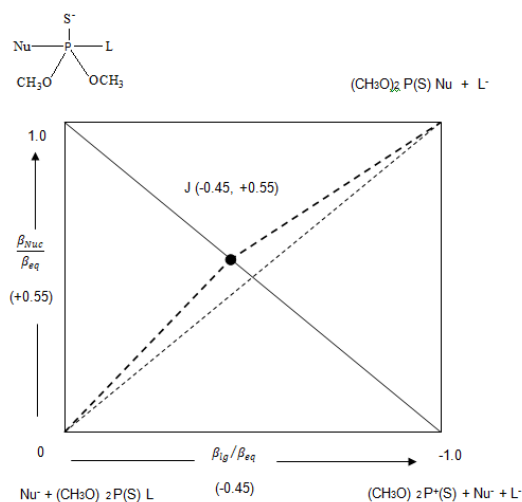

Fig. 4. More O'Ferrall-Jencks diagram for the transfer of the dimethylthiophosphoryl group between the 3-methyl-4-nitrophenoxide leaving group and the phenoxide nucleophiles. Bond formation and fission are measured by the appropriate Leffler parameter $\propto_{(bondformation)} = \beta_{Nu}/\beta_{eq} = 0.403/0.734 = 0.55$ and $\propto_{(bondfission)} = \beta_{lg}/\beta_{eq} = -0.331/0.734 = -0.45$ in 100% water at 25°C. The point J represents the position of the transition state for the symmetrical reaction
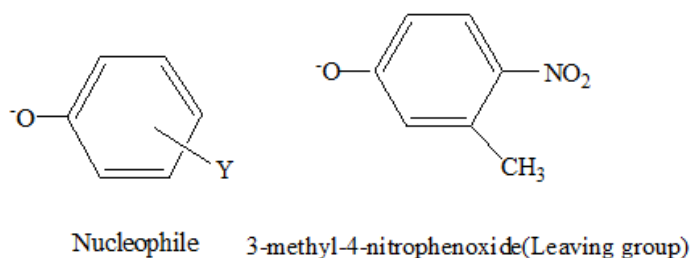
Fig. 5. Nucleophile and leaving group

and the degree of leaving group bond rupture, $\propto_{(br)} = \frac{\beta_{lg}}{\beta_{eq}}$ are calculated to be 0.55 and - 0.45, respectively. The position of the TS in the reaction map (Fig. 3) is located by the values of $\propto_{(bf)}$ and $\propto_{(br)}$ as J along the tightness diagonal (Albery and Kreevoy, 1978) or disparity reaction [12]. This position is slightly shifted away from the intersection of the synchronous route and the tightness diagonal, thus confirming that the reaction under consideration is a concerted one in which bond formation is only slightly advanced over bond breaking in the TS. This result is inconsistent with the presence of a discrete pentacoordinate intermediate, since such an intermediate will be too unstable to have any real existence at this point of the energy surface.

4. CONCLUSION

The applications of available mechanistic criteria have led different groups of researchers to suggest mainly two types of mechanisms for nucleophilic displacement at a phosphorus center; the concerted one step S_N2 type mechanism and the stepwise mechanism involving an intermediate.

The Brønsted-type plot of log k_{Nuc} versus pKa_{Nuc} reports statistically acceptable linear correlations for a selection of substituted phenoxide ions over a range that straddles the pKa of the leaving, 3-methyl-4-nitrophenoxide ion. i.e.

$$logk_{Nuc} = (0.403 \pm 0.01)pKa - 5.971 \pm 0.08 \quad (R^2 = 0.987 \; n = 5)$$

where R^2 is the correlation coefficient and n is the number of data points observed. The results are consistent with a concerted projection i.e. mechanism involving a single transition state or one whose barrier to decomposition is way too low. The slope of the Brønsted-type plot, β_{Nuc}, for the reaction of selected substituted phenoxides

with fenitrothion was observed to be 0.403. This simply shows that the nucleophilic displacement is sensitive to the basicity of the nucleophile and the Brønsted type free linear energy relationship supported that the reaction mechanism for nucleophilic displacement at the phosphorus center of fenitrothion by a series of substituted phenoxide ions at 25°C is a concerted one of the S_N2 type. The transition state location on the More O'Ferrall-Jencks diagram was found to be on the tightness diagonal, slightly above the point of intersection (+0.50, -0.50) with the leffler parameters given by $\propto_{(bondformation)} = 0.55$ and $\propto_{(bondfission)} = -0.45$. The position of J on the diagram shows that the reaction is concerted of the S_N2 type hence quenching the ambiguity in literature about the mechanism of the nucleophilic reactions of aryl phosphorothioates.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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