Concerted rate-limiting proton transfer to sulfur with nucleophilic attack at phosphorus — A new proposed mechanism for hydrolytic decomposition of the P=S pesticide, Diazinon, in moderately acidic sulfuric acid media

Doreen Churchill, Julian M. Dust, and Erwin Buncel

Abstract: We report herein the first kinetic study of a P=S containing organophosphorus pesticide, Diazinon (**1**), in the moderately concentrated acid region. Product analyses (^{31}P NMR) show that reaction occurs only at the P centre. The rate-acidity profile (k_{obs} vs. molarity of H_2SO_4) appears as a curve in which the initial slight downward trace (molarity = 1 to ca. 5) is followed by sharper upward curve (molarity ca. 5 to 14). Using treatments involving the excess acidity (*X*) method, the A-1 and A-2 mechanistic possibilities were found to be inoperative over the full acidity range. A novel mechanism is proposed for the higher acidity (*X* ca. 2–6) region. This mechanism involves proton transfer to P=S from hydronium ion with concomitant proton transfer from water, which effectively delivers hydroxide to the P centre in a variant of the A-S_E2 process. A putative A-2 mechanism in this region is supplanted by the proposed A-S_E2 variant where the cyclic array results in proton transfer being efficiently coupled with nucleophilic attack involving water. This constitutes the first report of rate-limiting proton transfer at the P=S functionality in acid hydrolysis of this class of organophosphorus neutroxins. A 600 000-fold acceleration in the decomposition of Diazinon is associated with the change of medium from neutral aqueous solution to the most acidic medium studied (*X* ca. 6).

Key words: phosphorothioate ester hydrolysis, acid catalysis, rate-limiting proton transfer at P=S, excess acidity analysis, new A-S_E2 variant mechanism.

Résumé : Dans ce travail, on présente les résultats de la première étude cinétique d'un pesticide organophosphoreux contenant une liaison P=S, le Diazinon (**1**), dans la région acide modérément concentrée. L'analyse des produits (RMN du ^{31}P) montrent que la réaction ne se produit qu'au centre réactionnel comportant le P. Le profile de la réactivité en fonction de l'acidité (k_{obs} vs. molarité de H_2SO_4) s'apparente à une courbe dans laquelle la pente initiale légèrement vers le bas (molarité allant de 1 à environ 5) est suivie par une courbe beaucoup plus prononcée vers le haut (molarité allant d'environ 5 à 14). Utilisant des traitements impliquant la méthode de l'acidité en excès (*X*), on a trouvé que les possibilités mécanistiques A-1 et A-2 ne s'appliquent pas à l'ensemble de la plage d'acidité. On propose donc un nouveau mécanisme pour la région supérieure d'acidité (valeur de *X* d'environ 2 à 6). Ce mécanisme implique transfert de proton à la liaison P=S à partir de l'ion hydronium avec un transfert concomitant de proton de l'eau qui permet de transférer d'une façon efficace l'hydroxyde au centre P dans un processus apparenté au mécanisme A-S_E2. Un mécanisme putatif A-2 dans cette région est supplanté par la variante A-S_E2 proposée lorsque les arrangements cycliques conduisent à un transfert de proton couplé à une attaque nucléophile impliquant de l'eau. Ceci correspond au premier rapport d'un transfert de proton cinétiquement limitant au niveau de la fonctionnalité P=S dans l'hydrolyse acide de cette classe de neutroxines organophosphorées. La décomposition du diazinon est 600 000 fois plus rapide lorsqu'on passe d'un milieu impliquant une solution aqueuse neutre au milieu plus acide étudié (*X* d'environ 6).

Mots-clés : hydrolyse d'esters phosphorothioates, catalyse acide, transfert de proton cinétiquement limitant au P=S, analyse par excès d'acidité, mécanisme nouveau, une variante du mécanisme A-S_E2.

[Traduit par la Rédaction]

Received 26 February 2007. Accepted 12 April 2007. Published on the NRC Research Press Web site at canjchem.nrc.ca on 8 June 2007.

This article is dedicated to the memory of Keith Yates, a good friend, who masterfully changed physical organic chemistry.

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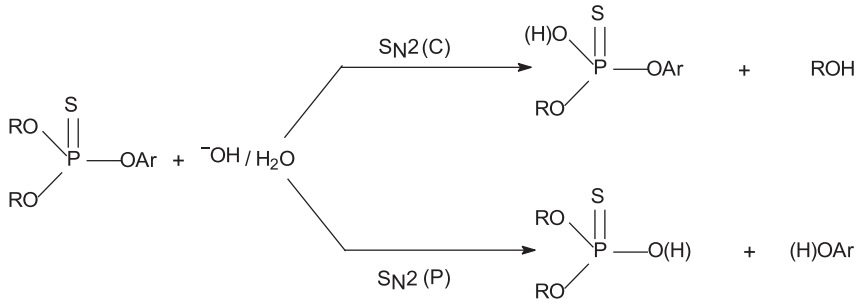
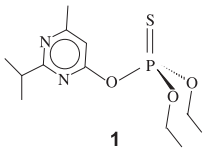
 doi:10.1139/V07-049

Scheme 1. Major reaction pathways of organophosphorothioate insecticides, where the protons in parentheses may or may not be present depending on the acidity of the medium.



Introduction

Diazinon (**1**) is a member of a class of organophosphorothioate insecticides whose mechanism of action is acetylcholinesterase inhibition (1). In principle, such esters may exhibit two main pathways of reaction in neutral or alkaline aqueous solution, as shown in Scheme 1, where hydroxide is taken to be the dominant nucleophilic species under alkaline environmental conditions (2, 3). As shown, the dichotomy of attack involves C or P centres. On the aliphatic carbons (R = CH_3 or CH_2CH_3, typically) an S_N2(C) displacement occurs to give the corresponding organophosphorothioate anion and the alcohol. Attack at phosphorus in a presumably S_N2(P) mechanism (4) produces the aryloxide as a leaving group and the organophosphorothioic acid or its conjugate base (Scheme 1).



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We, among other groups (5–7), have been engaged in the study of the degradation pathways and reactivities of a number of organophosphorus neurotoxins. In the case of fenitrothion (Scheme 1, R = CH_3, Ar = 3-methyl-4-nitrophenyl) with alkali metal ethoxides in ethanol, we dissected the pathways and found that S_N2(P) was dominant, S_N2(C) also contributed significantly, while the S_NAr attack on the aromatic ring constituted ca. 7% of the reaction (8). More recently (9), the regioselectivity of nucleophilic attack on fenitrothion was used to infer the location and orientation of fenitrothion in cationic micellar (9*a*) α-nucleophilic (9, 10) systems. These studies have highlighted the importance of the medium on pathways of reaction for these neurotoxins.

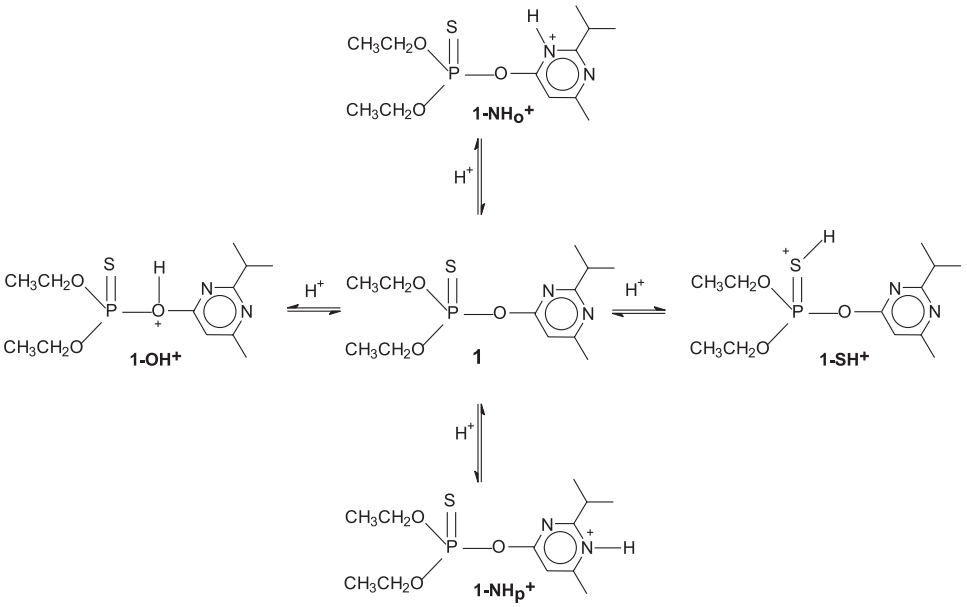
The research on Diazinon **1** (Scheme 1, R = CH_2CH_3, Ar = 2-isopropyl-6-methyl-pyrimidin-4-yl) for the most part has involved environmental studies, as it is an insecticide that has been applied for agricultural, silvicultural, and horticultural control of various insects (11). Most of these studies have focused on the half-life for disappearance of this insecticide in nonsterilized natural waters at various temperatures. Product analyses have emphasized biological breakdown rather than abiotic hydrolysis. In summary, few studies have examined the hydrolysis of **1** to fully elucidate reaction pathways of degradation in pure sterile water. However, a study by Ku et al. (12) involved the analysis of the products arising from hydrolysis under the pH range 2 to 9 and found 2-isopropyl-6-methylpyrimidin-4-ol (**2**) and *O*,*O*-dimethylphosphorothioate (or its conjugate acid) (**3**) as the only products.

One theme of our program of research has been the effect of reaction media on the reactivity and pathways of organic substrates (13), while the effect of acidic media (e.g., moderately concentrated sulfuric acid solutions) form a sub-theme (14). A third area of study in our group is environmental chemistry and the study of pesticide decomposition mechanisms (8, 9, 15). Our study of Diazinon **1** falls under this rubric. Our initial finding of a rate increase in the low pH region (16*a*) has now led to a study of the behaviour of **1** over a wide range of sulfuric acid solutions (H_2SO4 1–14 mol/L). Unlike previous work on organophosphorothioate ester degradation in alkaline media, the much weaker nucleophile H_2O will operate here. In this regard, attack at the aliphatic carbon could become more favourable here, since H_2O, as a softer nucleophile, would be expected to prefer attack at the softer carbon site (17).

In acidic media, the potential for catalysis would open up new and potentially faster pathways for decomposition. We note that the practical utility of acid hydrolysis of Diazinon formulations (that may also contain other bioactive agents) was examined by Dennis et al. (18) and emphasized the need for a mechanistic evaluation of such acidic systems. Scheme 2 highlights the multiplicity of protonation sites. Protonation of **1** on the aryloxy oxygen, giving rise to **1**-OH^+, would enhance the reaction by providing a better leaving group following the attack at phosphorus. Alternatively, protonation of the ring nitrogens of the pyrimidinyl moiety of **1** to give **1**-NH_o^+ or **1**-NH_p^+ would also produce a better leaving group and so may enhance the reaction. Protonation at P=S to give **1**-SH^+ would increase P electrophilicity, enhancing the attack by nucleophiles at phosphorus. Catalysis in moderately acidic media could be due to any one of these protonations or through the interplay of several simultaneously.

In this paper we report the acidity-rate constant profile for **1** in 1–14 mol/L sulfuric acid. The results will be discussed in terms of the excess acidity analysis, modes of acid catalysis, and potential mechanistic changeover (19, 20). The interesting rate-excess acidity profile has led us to propose a new variant of the A-S_E2 mechanism in the higher acidity medium in which rate-limiting proton transfer to the sulfur

Scheme 2. Protonation pathways of Diazinon.



of the P=S ester bond may occur in a concerted fashion with nucleophilic attack on the phosphorus centre.

Experimental

Materials and instruments

Common solvents and reagents (e.g., 95%–98% H_2SO_4, 99.8% D_2O, 85% H_3PO_4, and dimethyl sulfoxide-d_6) were purchased in the highest purity available and used without further treatment. Diazinon **1** was either obtained from Chem Services Inc. (99.5%) and used as obtained or synthesized as outlined later. *O*,*O*-diethylphosphorothioic acid **3** and triethyl thiophosphate were prepared in our laboratories and purified prior to use by column chromatography as described previously (16). Other reagents were purchased commercially but purified before use (vide infra).

Routine NMR spectra were recorded using a Bruker 300 MHz Avance spectrometer. For NMR spectrometric product analyses or kinetic studies, a Bruker 500 MHz Avance instrument was used. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. For UV–vis spectrophotometric measurements and for kinetic runs, the following instruments were used: Varian CARY 3, Hewlett-Packard 8452A, or PerkinElmer Lambda-20. Temperature was maintained at 25 °C with a Peltier effect device in the case of the CARY 3 or with a circulating water bath in the case of the other spectrophotometers.

Diazinon (1)

Synthesis

Diazinon was synthesized by a method modified from Gysin and Margot (21). First, a weighed quantity of **2** (5.0 g; 0.033 mol) was reacted with KOH (1.9 g; 0.034 mol) in hot absolute ethanol to generate the potassium salt of **2**. Excess ethanol was removed at reduced pressure (rotovap), and then benzene (70 mL) was added. The solution was distilled to azeotropically remove water; residual benzene was removed using a rotovap. Dry acetone (100 mL) was then added. To this solution was added diethyl chlorothiophosphate (6.20 mL; 0.039 mol), and the mixture was heated at ~35 °C for 2 days under nitrogen. The solution was cooled and filtered through Celite® to remove KCl. The solvent was distilled from the filtrate (rotovap) to give an oil that was purified by column chromatography using methylene chloride as eluent. Two fractions were recovered, the starting material and crude **1**. When dried, the crude **1** was found to contain a white solid impurity (possibly unmodified **2**). The crude sample was dissolved in hexanes (40 mL) and purified by extraction with H_2O (4 × 20 mL). The hexanes layer was dried with anhydr. $MgSO_4$ and filtered to remove the drying agent. The solvent was removed using a rotovap and dried further overnight under reduced pressure and at ambient temperature. The final product was obtained in 50% yield and its purity was verified by ^1H, ^{31}P, and ^{13}C NMR (*J*-modulated and DEPT) spectroscopy. All spectra were consistent with that of Diazinon and contained no peaks ascribable to impurities. ^1H NMR ($CDCl_3$, ppm) δ: 6.64 (s), 4.33 (d of q, $J_{H\text{-}H}$ = 7.1 Hz, $J_{H\text{-}P}$ = 11.2 Hz), 3.10 (sept, $J_{H\text{-}Hf}$ = 6.9 Hz), 2.47(s), 1.37 (t, $J_{H\text{-}H}$ = 7.1 Hz) and 1.30 (d, $J_{H\text{-}H}$ = 6.9 Hz). ^{31}P NMR δ: 61.5 (s). ^{13}C NMR δ: 176 (s), 170 (s), 165 (d, $J_{C\text{-}P}$ = 4.6 Hz), 107 (d, $J_{C\text{-}P}$ = 6.4 Hz), 65.6 (d, $J_{C\text{-}P}$ = 5.1 Hz), 37.7 (s), 24.5 (s), 21.8 (s), 16.2 (d, $J_{C\text{-}P}$ = 8.0 Hz).

*p**K**a Values for the conjugate acids of 1 (1-NH$_p^+$, 1-NH$_o^+$, 1-SH$^+$) and models*

Attempts were made to determine pK_a values for the conjugate acids of Diazinon (Scheme 2, **1**-NH_p^+, **1**-NH_o^+, **1**-SH^+) and of 2-isopropyl-6-methyl-4-pyrimidinol **2** using ^1H (side chain and ring protons), ^{31}P NMR, as well as UV–vis spectrophotometric measurements (λ = 230, 254, and 260 nm). Generally, the methods yielded the same average values for the macroscopic acidity constants. These determinations involved recording spectra of **1** in a series of H_2SO_4 solutions (1–18 or 1–14 mol/L), and relevant chemical shifts

(or λ_{max} values) were plotted against the $-H_0$ acidity function for the acid solutions; H_0 is anchored to the aqueous pH scale. From these titration curves (fitted using the Origin® 7.0 program) the macroscopic pK_a value for **1**-NH_p^+ and (or) **1**-NH_o^+ (= 2.40) was determined and found to be similar to that for the same site in the product 2-isopropyl-6-methyl-4-pyrimidinol measured in the same way (i.e., pK_a = 2.84), which is also similar to that reported for the same site in 2,6-dimethyl-4-pyrimidinol (3.06) (22). These studies also set a limit for the pK_a ascribable to diprotonation at –7.3; higher acidity solutions led to the rapid decomposition of **1** and precluded a more precise assessment. A comparable ^{31}P NMR titration of *O*,*O*-diethyl phosphorothioic acid **3** yields a value for pK_a of the conjugate acid (S-site) of –5.14.

Purification of solvents and reagents and preparation of stock solutions

2-Isopropyl-6-methyl-4-pyrimidinol (2)

Commercial **2** (Sigma-Aldrich, 99%) was recrystallized from either acetone or ethanol to remove a fine black solid impurity. Melting point 172–173.5 °C (lit. value 172–175 °C (23)). The ^{1}H NMR spectrum (300 MHz) contained no extraneous peaks; (D_2O, ppm) δ: 6.09 (s, 1H, ring H-3), 4.72 (sept, 1H, *J* = 7.0 Hz, CH of 2-isopropyl), 2.19 (s, 2H, 6-CH_3), 1.19 (d, 6H, *J* = 7.0 Hz, CH_3 of 2-isopropyl). Exchange of the OH proton with solvent precludes its observation.

Stock solutions

In general, all stock solutions were prepared in volumetric flasks sealed with rubber septa or, alternatively, with a glass stopper and Parafilm®. Aqueous solutions were prepared with distilled, deionized, and degassed water (9). All stock solutions were stored in a refrigerator.

Sulfuric acid solutions

In each case, the calculated required amount of purified water was first transferred to the volumetric flask, and then the H_2SO_4 solutions were made up by mass. In general, the flasks were cooled in an ice bath and the calculated amount of concentrated (ca. 98%) H_2SO_4 was weighed and slowly added. The acid solutions were titrated against NaOH that had been standardized against anhydrous potassium hydrogen phthalate.

Diazinon (1)

An aliquot (15 μL) of **1** was dissolved in purified 1,4-dioxane (5 mL) to give the stock solution (1.10×10^{-2} mol/L). The 1,4-dioxane was purified prior to use by standard methods (24) and stored until use under nitrogen at low temperature (ca. –10 °C, freezer).

UV–vis spectrophotometric kinetic studies of the decomposition of 1 in acidic media

All kinetic runs were carried out under pseudo first-order conditions with the concentration of acid in large excess relative to Diazinon **1**. For experiments that used the stock solution of **1** in 1,4-dioxane, an aliquot (20 μL) of the stock solution was injected (via 25 μL gas-tight syringe) into the quartz UV cuvettes containing the sulfuric acid solution (2.50 mL added by pipette) with an initial (time = 0) concentration of **1** of 8.73×10^{-5} mol/L. The monitoring of this reaction solution spectrophotometrically revealed two processes, an initial fast process followed by a slow one; these were ascribed, respectively, to decomposition of the dioxane and of the substrate **1**. The rate data, however, could be readily dissected to yield the separate rate constants (25). The latter were validated by preparation of reaction solutions (in large volume) free of dioxane and the kinetic results here showed good agreement with those for the slower process.

In either case the rate of appearance of product **2** was followed at 230 nm, the approximate wavelength of maximum absorbance for **2** (or protonated derivatives), under acidic conditions (increased to 234 nm at higher acid concentrations). Reactions were monitored for at least three half-lives and the absorbance at infinite time (A_∞) noted at 10 $t_{1/2}$. Plots of $\log(A_\infty - A_t)$ vs. *t*, using suitable spectrophotometric data as described earlier for systems in which dioxane was present, afforded the pseudo first-order rate constants k_{obs} reported herein.

^{31}P NMR spectrometric studies of the decomposition of 1 in acidic media

Kinetic studies

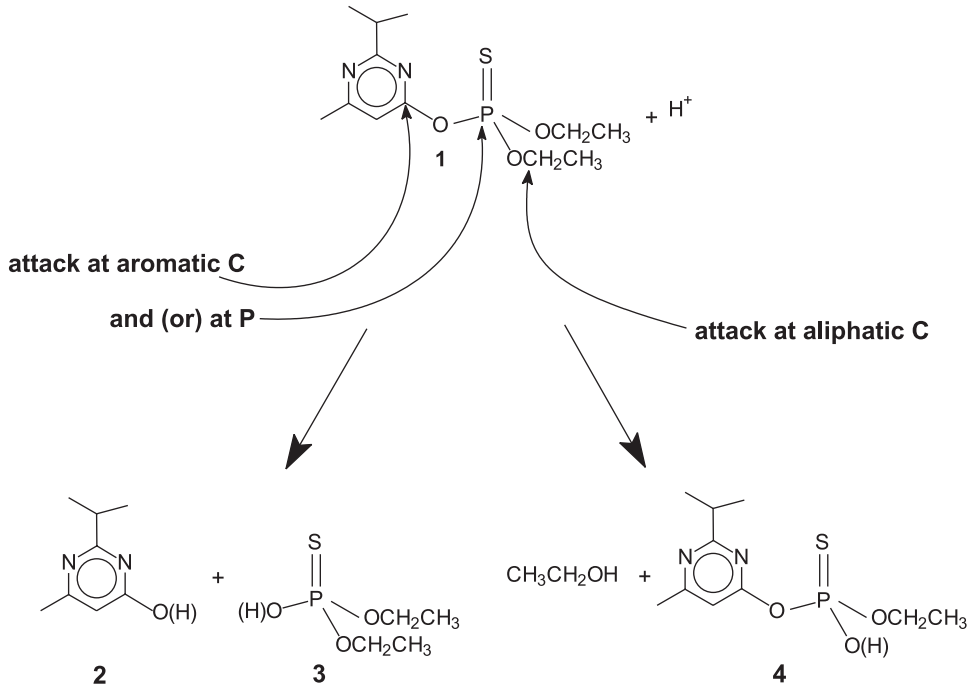
The reaction was initiated by addition of 4 μL of Diazinon (no solvent) to 1 mL of sulfuric acid solution (4.9–9.5 mol/L) in an NMR tube containing a sealed capillary tube that contained either 5% (*v*/*v*) trimethyl phosphate in DMSO-d_6 or 20% (*v*/*v*) 85% phosphoric acid in D_2O; these capillaries served as external chemical shift standards and supplied the needed lock signal. Spectrometric parameters were optimized (e.g., suitable relaxation delays are given in ref. 26) as previously reported (9). After placement of the tube in the probe of the NMR (at 25 °C), spectra were acquired at regular intervals and the rate constant determined on the basis of the integral of the ^{31}P NMR signal for Diazinon and that of the product signal (normalized versus trimethyl phosphate or phosphoric acid). The plot of natural log (signal area) vs. time yielded the rate constant k_{obs} according to a first-order treatment,

$$[1] \quad \ln(\text{Integral } \mathbf{1}_{initial} - \text{Integral } \mathbf{2}_{time}) = -k_{obs}t + \text{constant}$$

Product analysis

NMR tubes were prepared as outlined for the kinetic experiments. Each tube contained a concentration of sulfuric acid (ranging from 1 to 17 mol/L). The reaction was initiated by injection of 4 μL of **1**. The lower acidity tubes (1–13 mol/L) were set aside to permit reaction for 48 h, while the reaction was allowed for 20 min for the higher acidity (14–17 mol/L) samples. Once the reaction was deemed complete, a ^{31}P NMR spectrum was obtained. Only one product peak was observed; its identity was confirmed as *O*,*O*-diethylphosphorothioic acid **3** through spiking the tubes with authentic compound and re-recording the ^{31}P spectrum.

Scheme 3. Pathways of Diazinon hydrolysis under acidic conditions, where attack at aromatic carbon and (or) phosphorus contrasts with attack at aliphatic carbon.



Results

Acid-catalyzed hydrolysis of Diazinon 1 — UV–vis kinetic study.

Rate data for the hydrolysis of Diazinon in 1–14 mol/L H_2SO_4 solutions were determined spectrophotometrically by following the production of the pyrimidinol leaving group **2** (Scheme 3). The observed rate constants k_{obs} at 25 °C were calculated through application of eq. [2],

$$[2] \qquad \log (A_\infty - A_t) = -k_{obs}t + \text{constant}$$

where A_t is the absorbance at time t and A_∞ at infinite time (i.e., 10 $t_{1/2}$). The pseudo first-order rate constants for the decomposition of **1** at each sulfuric acid concentration and corresponding excess acidity X are given in Table 1.

^{31}P NMR study — Kinetics and product identification.

The reaction was also studied by ^{31}P NMR spectrometry, a method that provides simultaneous rate and product identification data. The pseudo first-order rate constants k_{obs}, in the H_2SO_4 range 4.9–9.5 mol/L, were calculated from the integration of the peak area of **1** or its P-containing product according to eq. [1] (see Experimental section).

The rate data obtained from ^{31}P NMR spectrometry (Table 1) were in good agreement with results using UV–vis spectrophotometry. ^{31}P NMR spectrometry also demonstrated that the only phosphorus-containing product of Diazinon hydrolysis is *O*,*O*-diethylphosphorothioic acid **3** (Scheme 3).

Table 1. Kinetic data for the acid-catalyzed hydrolysis of Diazinon in H_2SO_4 solutions at 25 °C.

$[H_2SO_4]$ (mol/L)	X^a	k_{obs} ($\times 10^{-4}$ s^{-1})^b	$t_{1/2}$ (min)
1.03[c]	0.22	0.686±0.007	168
2.26[d]	0.56	0.349±0.001	331
3.51[c]	0.96	0.174±0.006	663
3.63[d]	1.01	0.170±0.006	676
4.92[e]	—	0.152±0.008	760
4.99[c]	1.51	0.164±0.003	704
5.23[d]	1.60	0.156±0.006	736
6.50[c]	2.10	0.337±0.001	343
6.67[e]	—	0.320±0.016	361
6.85[c]	2.24	0.334±0.007	349
7.64[c]	2.57	0.558±0.001	207
7.64[e]	2.57	0.536±0.027	216
8.43[e]	—	1.04±0.05	111
8.57[c]	2.97	1.05±0.01	110
9.48[c]	3.39	2.15±0.01	53.7
9.48[e]	3.39	2.30±0.12	50.2
10.8[c]	4.07	4.89±0.03	23.6
11.7[c]	4.59	18.2±0.2	6.35
12.9[c]	5.35	90.6±0.70	1.28
13.9[c]	6.03	615±14	0.19 (11 s)

Discussion

Overview

The rate constants determined for the decomposition of **1** in moderately acidic media (Table 1, UV–vis determinations) were plotted as k_{obs} vs. the concentration of sulfuric acid (mol/L) (Fig. 1) and also plotted as log k_{obs} vs. the excess acidity function X, as the appropriate measure of the acidity of the medium (19, 27, 28) (Fig. 2). While the full scale plot in Fig. 1 (1 – ca. 14 mol/L) appears almost flat until about 11 mol/L where the curve swings upward, an enlargement (Fig. 1 inset) of the lower acidity region (1–8 mol/L) more clearly shows the initial decline in rate with

Fig. 1. Plot of pseudo first-order rate constants k_{obs} vs. sulfuric acid concentration (mol/L) for the hydrolysis of **1**. The enlarged inset of the concentration region from ca. 1 to 8 mol/L shows the initial decline and subsequent rise in reactivity with sulfuric acid concentration.

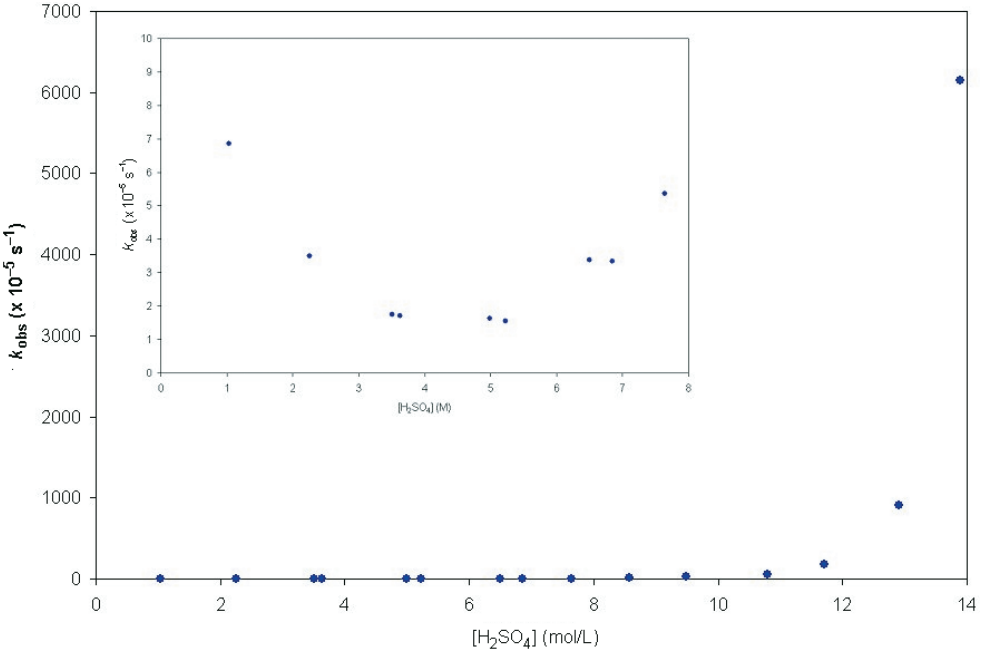
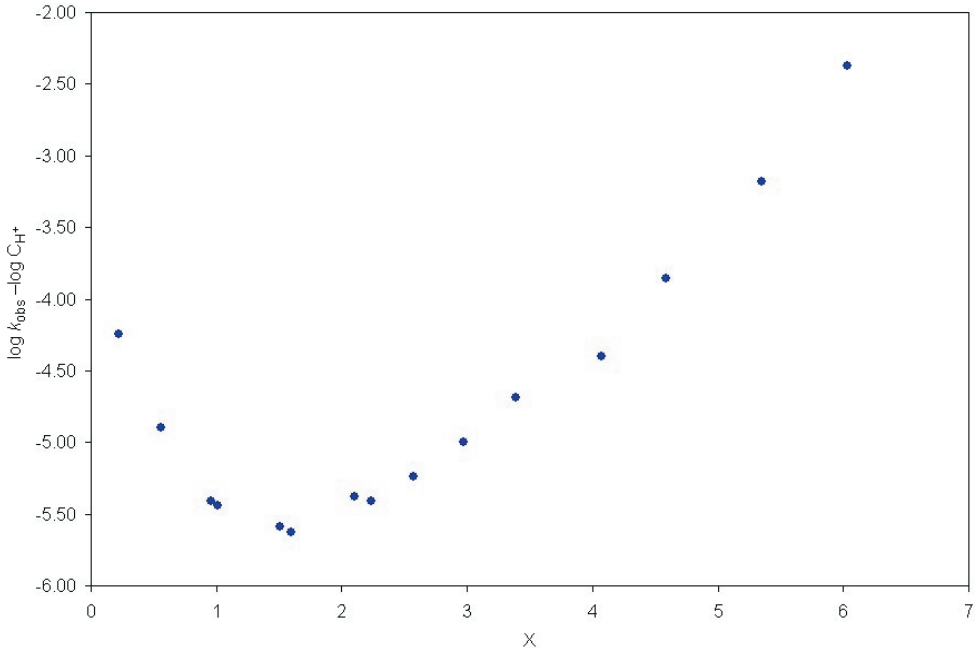


Fig. 2. Rate-excess acidity plot (log k_{obs} – log concentration of H^+ vs. X) for the hydrolysis of **1**.



increasing sulfuric acid concentration (1–5 mol/L), with the sharper increase commencing at a concentration of about 5 mol/L. The profile in Fig. 2 highlights this interesting initial decline in rate with increasing sulfuric acid concentration (X = 0–1.6). Note, however, that even the lowest reaction rate determined (k_{obs} = 1.52 × 10^{-5} s^{-1} corresponding to X ~ 1.6) is 150-fold greater than the rate previously reported at pH 7.0 (k_{obs} = 1 × 10^{-7} s^{-1} (29)). From X = 1.6 onward, the rate rises more steeply; a rate constant of 6.15 × 10^{-2} s^{-1} is attained at X ~ 6, the most acidic solution studied (13.9 mol/L H_2SO_4), i.e., an acceleration of the rate of decomposition by a factor of 600 000 as compared with that found at pH 7.0. These results, and especially the initial decline in rate constant with acidity and later steep rise in reactivity, suggest the intervention of more than one mechanism over this acid range.

As noted earlier, Diazinon contains several sites for potential protonation and these are identified in Scheme 2 as **1**-OH^+, **1**-SH^+, and **1**-NH_o^+ and **1**-NH_p^+ for the ortho- and para-nitrogens, respectively. By considering suitable model

compounds (e.g., pyrimidinol derivatives (30)), protonation of one of the ring nitrogens would plausibly be expected for monoprotonation. It is then also plausible to expect the formation of **1**-NH_p^+ to be favoured over the formation of the isomeric **1**-NH_o^+. (Also see the Experimental section where NMR and spectrophotometric titrations yielded a macroscopic pK_a of 2.40 for **1**-NH_p^+ and **1**-NH_o^+ and a limiting composite pK_a of –7.3 for diprotonation). Henceforth, therefore, in the acid media examined, **1**-NH_p^+ is taken as the starting species for further reaction.

Reaction pathways

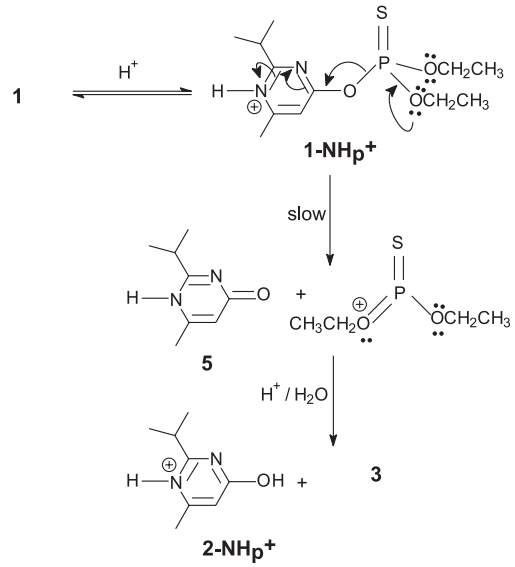
For the hydrolysis of Diazinon, three possible reaction sites can be envisioned; these include an attack at phosphorus as well as an attack at carbon, as outlined in Scheme 3. Attack at the aliphatic carbon of **1** would produce ethanol and de-ethyl Diazinon (**4**) as products; however, ^{31}P NMR spectrometry did not detect any **4**, and hence this pathway will not be considered further. This leaves the possibilities of attack at the aromatic carbon and (or) at phosphorus.

Considering first the S_NAr pathway, we note that generally two or more strongly electron-withdrawing substituents, such as nitro groups in the aromatic ring, are required for this route to be favoured. For example, in the case of the reaction of methyl 2,4-dinitrophenyl phosphate monoanion with amines, where nucleophilic attack at phosphorus is electrostatically suppressed, the reaction follows the S_NAr path (31). Differences in the reactivity of comparable P=S esters, as compared with this P=O example, would be expected to have little effect on this result (32). In contrast, with fenitrothion (Scheme 1, R = CH_3, Ar = 3-methyl-4-nitrophenyl) reacting with ethoxide, where the aryl ring of the leaving group is activated with only a single nitro group and where P-attack is not suppressed, ethanolysis via S_NAr occurs to a small (ca. 7%) extent, and P-attack is the dominant route (8). Thus, considering that a ring nitrogen is normally less effective in promoting S_NAr displacement compared with NO_2 (33), albeit recognizing that an unprotonated N is less activating than protonated N, it is reasonable to conclude that the reaction of Diazinon should proceed preferentially via P-attack rather than by S_NAr. Further discussion will, therefore, focus on reaction of **1** at the P-site.

Mechanisms of acid catalysis

In acidic media, reactions are most commonly catalyzed via mechanisms classified according to types A-1, A-2, or A-S_E2 (19, 27, 28*a*, 34–36). An A-1 process involves a unimolecular rate-determining step, where fast equilibrium protonation of the substrate S results in the formation of a reactive intermediate SH^+. In the current system, protonation facilitates the departure of the leaving group and SH^+ decomposes unimolecularly, and so here the A-1 pathway would involve the unimolecular breakdown of **1**-NH_p^+ with the formation of a metaphosphate-like intermediate, stabilized by resonance, that reacts further with water to give **3** (Scheme 4). On the other hand, in the A-2 mechanism fast equilibrium protonation of the substrate enhances the attack

Scheme 4. A-1 type mechanism for hydrolysis of Diazinon.



of a nucleophile in the bimolecular rate-determining step. Here, the rate-determining attack of water on the monoprotonated substrate 1-NH_p^+ with concomitant P–O bond scission leads to a protonated form **3**-H^+ that equilibrates to give **3** as the final product (Scheme 5). In contrast, *rate-limiting protonation* leading to the SH^+ intermediate that then decomposes in a separate fast step comprises the A-S_E2 pathway. A variant of this mechanism is proposed below.

The excess acidity treatment affords insight into the mechanistic pathways of acid catalysis.

A-1 process

For an A-1 mechanism (Scheme 4), the appropriate excess acidity relationship is expressed in eq. [3], where it is assumed that any diprotonation over the range of H_2SO_4 studied will be negligible (19),

$$[3] \qquad \log k_{obs} - \log C_{H^+} = \log[k/K_{SH_2^{++}}] + m^{\ddagger}m^{*}X$$

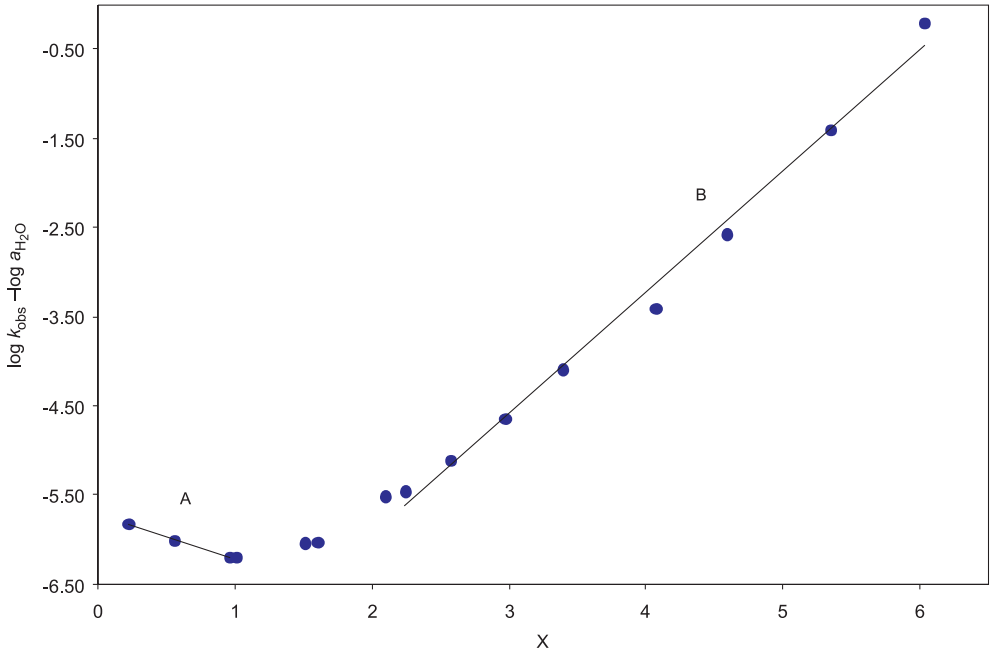
However, as Fig. S4 (Supplementary material) shows, the resultant plot, instead of being linear with positive slope, displays strong curvature with a broad minimum (at values of *X* between 1 and 2), thus ruling out this mechanism as the sole process involved in the current system throughout the range of acidity studied.[3] The plot could be described as a "broad upward parabola".

A-2 process

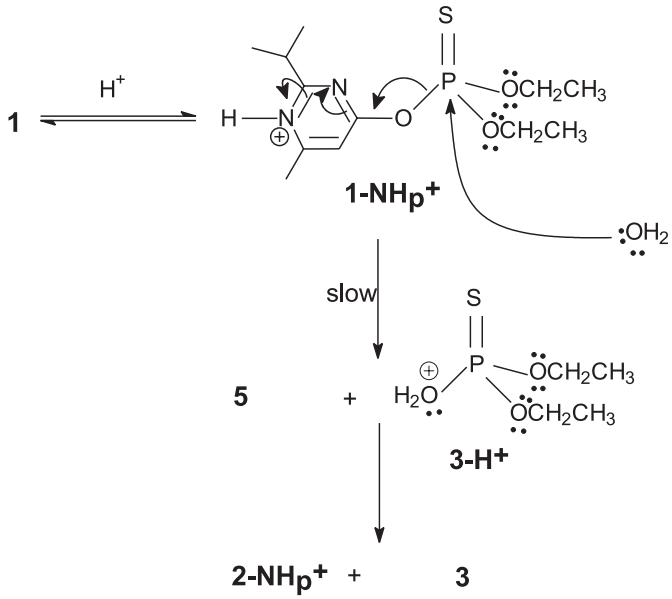
A-2 mechanistic types have been observed in a number of systems involving phosphorus-containing substrates (36–38). In an A-2 process one or more molecules of water may be involved in a rate-determining step that occurs after rapid equilibrium protonation of the substrate (19). Scheme 5 shows the case where a single molecule of water acts as nucleophile. For an A-2 mechanism, any general excess acidity plot (i.e., one obtained from an equation similar to eq. [3]) should yield a downward arc that achieves a maxi-

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5175.

Fig. 3. Rate-excess acidity plot for the hydrolysis of **1** showing a possible mechanistic switch from an A-2 process (line A) at lower X values to an A-1 (or A-S_E2 variant) process (line B) at higher X values. The equations of the lines are given in the text.



Scheme 5. A-2 type mechanism for hydrolysis of Diazinon.



mum near the point where the acidity of the medium would have fully converted the substrate to its protonated form. The decrease in rate that occurs with increasing acidity reflects the decreasing activity of water (a_{H_2O}) at higher acid concentrations.

The kinetic data were treated using eq [4], which involves one water as nucleophile (i.e., Nu = H_2O), and eq. [5], which involves two waters, neither of which however, yielded linear plots (Figs. S5 and S6; see Supplemental Data).[3]

$$[4] \quad \log k_{obs} - \log C_{H^+} - \log a_{Nu} = \log[k/K_{SH_2^{++}}] + m^{\ddagger}m^{*}X$$

$$[5] \quad \log k_{obs} - \log C_{H^+} - 2\log a_{Nu} = \log[k/K_{SH_2^{++}}] + m^{\ddagger}m^{*}X$$

However, even though the entire data do not fit either a single A-1 or A-2 mechanism, it is plausible that there is a change in mechanism when the plot switches from a decrease in rate with increasing acid concentration to an increase in rate with increasing acid concentration.

Switch from an A-2 to an A-1 process

Based on the pK_a values found for Diazinon (2.40 for **1**-NH_p^+ and **1**-NH_o^+ and –7.3 as a limit for diprotonation), it was presumed (vide supra) that Diazinon was protonated at all values of X studied and that **1**-NH_p^+ was, therefore, the starting species for any further discussion. It follows then, that instead of finding a full downward arc, as expected for an A-2 process, the region of the rate-excess acidity profile bounded by $X = 0$ to about $X = 2$ represents the portion of the expected A-2 process where the rate declines as a function of the decreasing amount of free water present. In effect, the expected A-2 arc is truncated so that only the downward portion is seen. An empirical straight line, using one molecule of water as the simplest case (Fig. 3), was fit to the data ($X = 0$ to ca. 1), and for the limited number of points involved the fit is good ($r^2 = 0.998$). The equation of the line is,

$$[6] \quad \log k_{obs} - \log a_{H_2O} = -0.493X - 5.721$$

Similarly, the region defined by $X = 2$ to about 6 yields an empirical straight line treatment (Fig. 3) where the fit is also good ($r^2 = 0.992$) and the equation of the line is,

$$[7] \quad \log k_{obs} - \log a_{H_2O} = 1.366X - 8.688$$

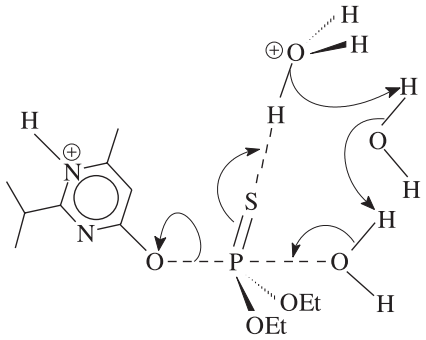
This second line could represent an A-1 mechanism, and therefore overall there would be a switch from an A-2 to an A-1 type mechanism. Such changeovers are far from unprec-

edented and are found for a number of esters, thiobenzoate, and thionobenzoate esters, among other systems (19, 27). However, there is a paucity of examples of acid catalysis of the breakdown of P=S pesticides with structures clearly analogous to **1** (36) in the higher acidity (*X* ca. 2–6) region, and hence, comparison to related systems cannot be made. Moreover, it is difficult to envisage the mechanism of A-1 *catalysis* with increasing acidity, since with **1** the initial N-protonation of the ring is already complete in the dilute acid region. In short, while it is apparent that the A-2 mechanism should become less effective as the concentration of free water declines, it is not apparent that the A-1 mechanism should lead to catalysis as the acidity of the medium increases.

A concerted rate-limiting proton transfer to S with nucleophilic attack at P — An A-S_E2 variant mechanism

An essential part of the reactivity of Diazinon must be associated with the P=S moiety (32). However, it is noteworthy that neither the A-2 nor A-1 mechanisms involve protonation of P=S, even though these mechanisms do not explain the kinetic behaviour throughout the full acidity range.

As a variant of the A-S_E2 class, a mechanism can be proposed where rate-limiting proton transfer to the P=S function occurs in a cyclic array involving hydronium ion as proton donor to S but as proton acceptor from water, which effectively delivers hydroxide to P. A transition state structure for this A-S_E2 variant mechanism is illustrated in structure **6**, where the dotted lines indicate partial bond formation and rupture. In this structure, a bridging water molecule is included as has often been found in such acid-catalysed hydrolyses.[4] To our knowledge, this would be the first instance in which rate-limiting proton transfer to S in a molecule containing the P=S functionality has been proposed.



6

On the other hand, a comparison can be made with the pertinent studies of Cox and Yates (39) on the hydrolytic decomposition of a range of three sets of SC=O and OC=S substrates: four thiobenzoic acids (Ar-CO-SH), eight ethyl thiobenzoates (Ar-CO-SCH_2CH_3), and eight ethyl thionobenzoates (Ar-CS-OCH_2CH_3) in aqueous sulfuric acid media. In general, all of these substrates exhibited two (or more) mechanisms of decomposition. For example, with the parent ethyl thiobenzoate three mechanistic regions could be defined: (*i*) an A-2 mechanism involving two water molecules (*X* ca. 1–2), (*ii*) an A-S_E2 region where hydronium ion was found to be the proton source (*X* ca. 2.5–4) that switches over to (*iii*) an A-S_E2 mechanism where the proton source was assigned to undissociated sulfuric acid (*X* ca. 5–10). In contrast to the behaviour of ethyl benzoate that follows an A-2 mechanism that changes over to an A-1 pathway at about *X* = 6 with acylium ion formation, all of these S-containing substrates exhibit mechanistic changeover at significantly lower acidities (ca. *X* = 2–3) (39). Note that the mechanistic switch (A-2 → A-S_E2) suggested here for Diazinon also occurs at an excess acidity value (*X*) of about 2. Cox and Yates (39) concluded "that proton transfer to sulfur in involved in the slow step of the reaction at least some of the time, for all three types of sulfur-containing substrate in the study" This conclusion may also extend to **1** in moderately acidic sulfuric acid media.

Returning to the Diazinon – aq. H_2SO_4 system, in a (hypothetical) A-2 mechanism involving protonation at S, the pK_a of the P=S group is a dominant consideration. Such protonation in the current system corresponds to protonation at S of the monoprotonated substrate, **1**-NH_p^+, i.e., diprotonation overall. In our estimate (see the Experimental section), the lower limit for the pK_a for diprotonation is –7.3. Therefore, the acidity in our study should be insufficient to produce diprotonation. Note as well that *O*,*O*-diethyl thiophosphoric acid, a model for protonation at P=S, was found to have a pK_a of –5.14. Unfortunately, Diazinon undergoes rapid degradation in media with higher acidities.

An important aspect concerning the proposed (A-S_E2) mechanism, which is to be emphasized, is that the concerted nature of the process makes it accessible in a lower acid region compared to the A-2 mechanism discussed above. In this acid region (*X* = 2–6), although a_{H_2O} continues to decline, this is more than compensated for by the increasing acidity, as evidenced by the sharp upward curve of the rate-excess acidity profile.

Since P=S is a defining feature of a large class of pesticides in use, and the proposed mechanism is directly tied to this structural feature, a broad avenue is opened for the study of the general behaviour of these biocides in acid media.

Conclusions

Whereas in pesticides the lowered hydrolytic activity of P=S triesters relative to their P=O analogues confers lowered mammalian toxicity on these biocides (1), this lowered reactivity opens up the possibility of other routes of reaction. In the current case, we propose that acid catalysis occurs via the less common A-S_E2 type rather than the traditional A-2 or A-1 paths outlined (Schemes 4 and 5). Therefore, in simple ester or amide hydrolysis in acid, the A-2 or changeover of A-2 to A-1 mechanisms (19, 27) are supplanted in Diazinon hydrolysis by the concerted variant of the A-S_E2 process involving partial rate-determining proton transfer to P=S from hydronium ion with concomitant proton transfer from water and effective attack of hydroxide at the P centre

[4] We thank a referee for drawing our attention to this point. The current treatment does not permit definitive assignment of the number of water molecules involved in the transition state.

(structure **6**). In nature, for example in enzymatic processes (e.g., chymotrypsin), rate-determining proton transfers involving relays, in which proton transfer is central to the catalysis are the norm.

Acknowledgements

Financial support of this work was provided by the Natural Sciences and Engineering Research Council of Canada (to EB) and PGS A and PGS B scholarships (to DC) are gratefully acknowledged. Thanks are also extended to the sponsors of the Pestcon Scholarship (granted to DC) administered by the Chemical Institute of Canada, which assisted these studies in pesticide chemistry. Support of the Sir Wilfred Grenfell College Principal's Research Fund (to JMD) is also noted. Helpful comments of the referees are cheerfully acknowledged.

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