(t, $J$ = 6.5 Hz, 3 H, Me in the chain).

**(*E*)-2-Penten-1-yl acetate (13)**: $^1$H NMR $\delta$ 5.84 (dt, $J$ = 14, 5.5 Hz, 1 H, H3), 5.56 (dt, $J$ = 14, 6 Hz, 1 H, H2), 4.52 (d, $J$ = 6 Hz, 2 H, H1), 2.15-1.98 (m, 2 H, H4), 2.06 (s, 3 H, OAc), 1.01 (s, 3 H, Me). The product was further characterized by hydrolysis to 2-penten-1-ol.[43]

**2-Methyl-3-buten-1-yl acetate (14)**: $^1$H NMR $\delta$ 5.70 (m, 1 H, H3), 5.11 (d, $J$ = 10 Hz, 1 H, $H4_{cis}$), 5.06 (d, $J$ = 17 Hz, 1 H, $H4_{trans}$), 3.97 (d, $J$ = 6 Hz, 2 H, H1), 2.52 (m, 1 H, H2), 2.06 (s, 3 H, OAc), 1.27 (d, $J$ = 6 Hz, 3 H, Me2). The product was further characterized by hydrolysis to 2-methyl-3-buten-1-ol.[43]

**(*E*)-2-Octen-1-yl acetate (15)**[44] (from a mixture with **16**): $^1$H NMR $\delta$ 5.78 (dt, $J$ = 15.5, 6.5 Hz, 1 H, H3), 5.65-5.53 (m (concealed), 1 H, H2), 4.51 (d, $J$ = 6.5 Hz, 2 H, H1), 2.36 (m, 2 H, H4), 2.06 (s, 3 H, OAc), 1.49-1.18 (m, 6 H, three methylenes in the chain), 0.90 (br t, 3 H, Me).

**2-(Ethenyl)hexyl acetate (16)**: $^1$H NMR $\delta$ 5.60 (m, 1 H, H1 in the ethylene chain), 5.06 (dd, $J$ = 12, 2 Hz, 1 H, $H2_{cis}$ in the ethylene chain), 5.05 (dd, $J$ = 17, 2 Hz, 1 H, $H2_{trans}$ in the ethenyl chain), 3.99 (d, $J$ = 6.5, 2 H, H1), 2.35 (m, 1 H, H2), 2.04 (s, 3 H, OAc), 1.49-1.15 (m, 6 H, three methylenes in the chain), 0.88 (br t, 3 H, Me).

**4-*n*-Butyl-2-cyclohexen-1-yl acetate (17)** (from a mixture with **18**): $^1$H NMR $\delta$ 5.76 (m, 2 H, olefinic), 5.31 (m, 1 H, H1), 2.12 (m, 2 H, allylic), 2.05 (s, 3 H, OAc), 1.98-1.53 (m, 4 H, H5 and H6), 1.45-1.15 (m, 6 H, three methylenes in the chain), 0.88 (br t, 3 H, Me).

**2-*n*-Butyl-3-cyclohexen-1-yl acetate (18)**: IR 2930, 1735, 1241, 608 cm$^{-1}$; $^1$H NMR $\delta$ 5.67 (ddd, $J$ = 10, 7, 3 Hz, 1 H, H4), 5.55 (ddd, $J$ = 10, 5, 1.5 Hz, 1 H, H3), 4.78 (ddd, $J$ = 9, 6.7, 3 Hz, 1 H, H1), 2.19 (m, 1 H, H2), 2.11 (m, 2 H, H5), 2.06 (s, 3 H, OAc), 1.94-1.82 (m, 1 H, $H6_{eq}$), 1.77-1.59 (m, 1 H, $H6_{ax}$), 1.48-1.19 (m, 6 H, three methylenes in the chain), 0.90 (br t, 3 H, Me); $^{13}$C NMR $\delta$ 170.88, 128.58, 126.22, 73.65, 40.14, 32.56, 28.55, 26.12, 23.23, 22.87, 21.40, 13.98. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.188; H, 10.11.

**(*E*)-5-Methyl-6-dodecene ((*E*)-20)** (from a mixture with (*Z*)-**20**): $^1$H NMR $\delta$ 5.34 (dt, $J$ = 15.5, 6 Hz, 1 H, H7), 5.23 (dd, $J$ = 15.5, 7 Hz, 1 H, H6), 1.99 (m, 3 H, allylic), 1.40-1.12 (m, 12 H, six methylenes in the chains), 0.93 (d, $J$ = 7 Hz, 3 H, Me5), 0.88 (m, 6 H, two Me). The *Z*-isomer (*Z*)-**20** is distinguishable in a mixture with (*E*)-**20** by its peaks at $\delta$ 5.10 (dd, $J$ = 10, 10 Hz, 1 H, CHC*H*=) and 2.40.

**(*E*)-(4-Methyl-2-octenyl)propanedioic acid dimethyl ester ((*E*)-22)** (from a mixture with (*Z*)-**22**): $^1$H NMR $\delta$ 5.38 (dd, $J$ = 15, 6.5 Hz, 1 H, C*H*=), 5.29 (dt, $J$ = 15, 6.5 Hz, 1 H, C*H*=), 3.72 (s, 6, two OMe), 3.47 (m, 1 H, $CH(COOMe)_2$), 2.70-2.52 (m, 2 H, $CH_2C$=), 2.02 (m, 1 H, H5), 1.36-1.08 (m, 6 H, three methylenes in the chain), 0.91 (d, $J$ = 7 Hz, 3 H, Me), 0.87 (t, $J$ = 5.5 Hz, 3 H, terminal Me). The *Z*-isomer (*Z*)-**22** is distinguishable in a mixture with (*E*)-**22** by its peak at $\delta$ 5.24 (m, 2 H, CH=CH).

**(*E*)-(2-(1-Propenyl)hexyl)propanedioic acid dimethyl ester (23)**: Spectral data were in accordance with those previously reported.[30]

**Acknowledgment**. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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# Oxidative Detoxification of Phosphonothiolates

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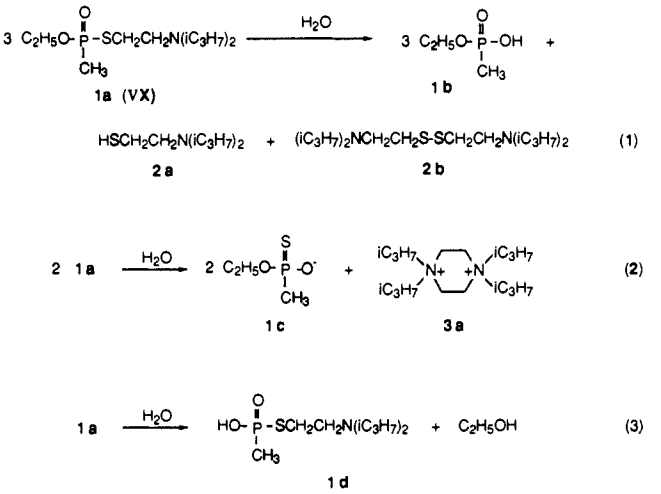
**Abstract:** The chemical nerve agent *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX) is an unusually selective oxidation substrate. Relative to the thiolo sulfur, the amino nitrogen was a more reactive oxidation site. The oxidation of VX and a phosphonothiolate derivative by a broad range of peroxygen compounds was examined in organic, polar organic, and aqueous solvents. Depending on the oxidant, VX was either unreactive or reactive via one of the following mechanisms: 1. In neutral solvents, the nitrogen was oxidized first to an *N*-oxide, which was stable in aqueous solvents but decomposed by a Cope reaction in organic solvents. 2. After the nitrogen had been oxidized or protonated in an acidic aqueous solvent, the sulfur in the *N*-oxide or the protonated VX was further oxidized to a sulfoxide intermediate, which hydrolyzed immediately. Detoxification can be accomplished by the second mechanism.

## Introduction

Most of the toxic organophosphorus esters can be detoxified quickly by hydrolysis in alkaline solutions.[1,2] However, relative to the chloro- or fluorophosphonates [RP(O)(OR')X, X = Cl or F], the hydrolysis of phosphonothiolate esters (X = SR'') is much slower even at very high pH values.[3,4] The estimated half-life for the spontaneous hydrolysis of the nerve agent VX, *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothiolate (**1a**), was 80 h at 20 °C. In addition, multiple hydrolysis pathways have been reported.[4] As shown in eqs 1-3, VX hydrolyzes via simultaneous cleavage of the P-S, S-C, and P-O bonds to form a series of products. Although both the ethyl methylphosphonic acid (**1b**) and the *O*-ethyl methylphosphonothioic acid (**1c**) are relatively nontoxic, the *S*-[2-(diisopropylamino)ethyl] methylphosphonothioic acid (**1d**) is almost as toxic as VX (see toxicity data in Table I in the Experimental Section). Contrary to the findings by Epstein et al.[4] that VX hydrolyzed via the single reaction path shown in eq 1 at pH values greater than 10, ~22% **1d** and 78% **1b** were produced from the reaction of 0.05 M VX

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(3) DeBruin, K. E.; Tang, C.-l. W.; Johnson, D. M.; Wilde, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 5871-5879.
(4) Epstein, J.; Callahan, J. J.; Bauer, V. E. *Phosphorus Relat. Group V Elem.* **1974**, *4*, 157-163.

with 2 N NaOH in an aqueous solution of 10 vol % 2-propanol (necessary to solubilize VX under alkaline conditions). This precludes base-catalyzed hydrolysis as an effective detoxification method.

It is the purpose of this study, therefore; to identify oxidation systems that are effective in detoxifying VX at room temperatures. Both the sulfur and the nitrogen in VX are potential sites for oxidation, which may lead to subsequent decomposition and detoxification of the compound. Only limited published work can be found on this subject.[5,6] It was generally believed that VX could only be oxidized by chlorine-based oxidants since bleach solutions have been used in the laboratory to decontaminate VX. However, the hypochlorite anion also acts as a base/nucleophile attacking the phosphorus.[7] The products generated were too complicated to provide insight into the oxidative reactivity of VX.[8]

In order to concentrate our investigation on the oxidation mechanism solely, all of the oxidants used in this work were free from chlorine. Stable commercial peroxygen compounds such as *m*-chloroperoxybenzoic acid (*m*-CPBA), *tert*-butyl hydroperoxide, and Oxone [active component, caroate ($KHSO_5$)][9,10] were used in protic solvents ranging from pure *tert*-butyl alcohol, and *tert*-butyl alcohol–water mixtures to pure water. The oxygen atom transfer mechanism of peroxides in the oxidation of amines and sulfides has been extensively studied.[9] In general, oxidation proceeds via a bimolecular displacement mechanism ($S_N2$) and is slower in protic solvents than in aprotic solvents. For the same oxidant, the reaction rate increases with the basicity of the S- or N-containing substrate. For the same substrate, the reaction rate increases with the stability of the leaving group of the oxidant. To further investigate the reaction mechanism, a selective, organic oxidant, *N*-sulfonyloxaziridine **4a**,[11] was also used to oxidize VX. Furthermore, under each of the above oxidation conditions, the oxidative reactivity of VX was compared with that of a simple phosphonothiolate derivative, *O,S*-diethyl methylphosphonothiolate (**1e** in eq 7; also see Table I for toxicity), so that the effect of the diisopropylamino group in VX could be ascertained. It was observed that while a significant amount of **1e** could be dissolved in pure water, it remained unchanged in solution for at least 7 months. **1e** is therefore hydrolytically unreactive and an excellent base-case substrate for oxidation studies in aqueous solutions.

Typically, $^{31}P$ NMR was used to monitor the oxidations at 19–21 °C. For fast oxidations, $^{1}H$ NMR was used for 0.0005 M substrate in a $D_2O$ solution. The reaction products were identified by both $^{31}P$ and $^{13}C$ NMR, GC/MS, and by direct exposure probe (DEP) mass spectrometry. Detailed experimental procedures and instrumentation are described in the Experimental Section, in which representative NMR spectral parameters and the GC/MS data for compounds identified are also listed separately in Tables II and III.

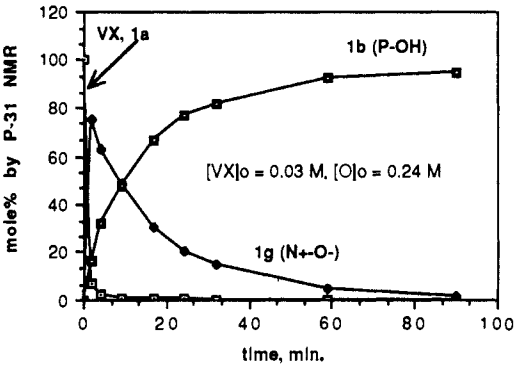
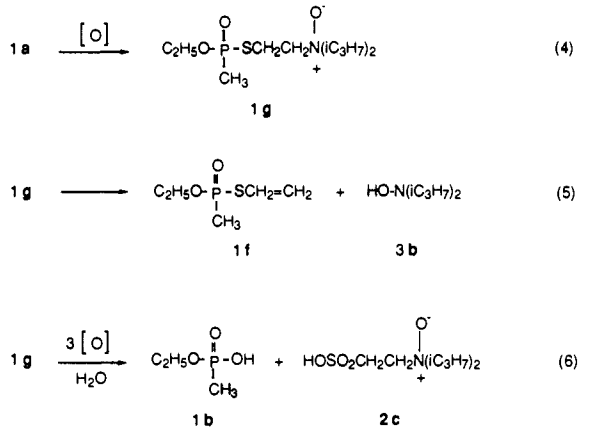



**Figure 1.** Oxidation of VX by *m*-CPBA in 50 vol % *tert*-butyl alcohol at 19 °C.

## Results and Discussion

**1. Oxidation of the Amino Nitrogen.** In pure *tert*-butyl alcohol as well as in a 50 vol % *tert*-butyl alcohol solution, an equal molar mixture of VX and *m*-CPBA (0.03 M) reacted instantaneously to form a stable *N*-oxide (**1g** in eq 4). In pure *tert*-butyl alcohol,




as shown in eq 5, **1g** subsequently decomposed to *O*-ethyl *S*-vinyl methylphosphonothiolate (**1f**) and diisopropylhydroxylamine (**3b**), apparently via a Cope reaction[12] with a half-life of approximately 2 h at 20 °C. As expected for an E1 mechanism, the decomposition half-life of **1g** was reduced to ~1 h in a less polar solvent system of equal volumes of benzene and *tert*-butyl alcohol, while only 10% of **1g** decomposed in the 50 vol % *tert*-butyl alcohol solution after 27 h.[13] The structures of both **1g** and **3b** were further verified by $^{13}C$ NMR with two model compounds, diisopropylmethylamine and isopropylhydroxylamine oxalate (**3c** and **3d**; see Experimental Section). This is the first time the VX *N*-oxide has been identified. Since the P–S bond is still present in both **1g** and **1f**, these compounds are believed to be toxic so that oxidation of the nitrogen, although a fast reaction, may not completely detoxify VX.

In the presence of excess *m*-CPBA in 50 vol % *tert*-butyl alcohol, as shown in Figure 1, VX was first converted to **1g**, which was subsequently oxidized at the sulfur followed by immediate hydrolytic cleavage of the P–S bond. Three equivalents of active oxygen ([O]) were consumed to oxidize the sulfur moiety in **1g** to the sulfonic acid **2c**. The reaction products, **1b** and **2c**, shown in eq 6 were nontoxic; VX was thus detoxified by *m*-CPBA. The two reactions shown separately in eqs 5 and 6 were consequently

(5) In a series of recent papers, the oxidation of a number of phosphorothiolate pesticides by *m*-CPBA in both protic and aprotic organic solvents were investigated; see: (a) Segall, Y.; Casida, J. E. *Phosphorus Sulfur Relat. Elem.* **1983**, *18*, 209–212. (b) Segall, Y.; Casida, J. E. *Tetrahedron Lett.* **1982**, *23*, 139–142.

(6) Thompson, C. M.; Castellino, S.; Fukuto, T. R. *J. Org. Chem.* **1984**, *49*, 1696–1699.

(7) (a) Epstein, J.; Bauer, V. E.; Saxe, M.; Demek, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 4046–4071. (b) Lori, N. G.; Epstein, J. *J. Am. Chem. Soc.* **1958**, *80*, 509–515. (c) Horner, L.; Gerhard, J. *Phosphorus Sulfur Relat. Elem.* **1985**, *22*, 13–21.

(8) Preliminary NMR studies in this laboratory show that VX can only be converted to the phosphonic acid **1b** by a large excess of the active chlorine from the bleach solution. The non-phosphorus products have not been identified. Sulfoxide, sulfone, and carbonyl groups may be present in these products.

(9) (a) For a review on peroxides and peracids, see: Curci, R.; Edwards, J. O. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 1, Chapter IV. Also see: (b) *The Chemistry of Peroxides*; Patai, S., Ed.; Interscience: Chichester, 1983; Chapters 5, 17. (c) For oxidation of sulfides, see: Block, E. In *Oxidation and Reduction of Sulphides, The Chemistry of Functional Groups*, Supplement E; Patai, S., Ed.; Interscience: Chichester, 1980; Part I, pp 539–608. (d) For oxidation of amines, see: Goldblum, A.; Loew, G. H. *J. Am. Chem. Soc.* **1985**, *107*, 4265.

(10) For a review on Oxone, see: Kennedy, R. J.; Stock, A. M. *J. Org. Chem.* **1960**, *25*, 1901–1907.

(11) (a) Davis, F. A.; Jenkins, R. H., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171–5174. (b) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem.* **1986**, *51*, 4240–4245. (c) Yang, Y.-C.; Szafraniec, L. L.; Beaudry, W. T.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3664–3666.

(12) (a) Cope, A. C.; Pike, R. A.; Spencer, C. F. *J. Am. Chem. Soc.* **1953**, *75*, 3212. (b) Cope, A. C.; Lebel, N. A.; Lee, H. H.; Moore, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 4720.

(13) After 27 h, **1g** also began to hydrolyze in the 50 vol % *tert*-butyl alcohol solution to produce **1b**, which was identified by $^{31}P$ NMR. The hydrolysis rate was slightly faster than VX, indicating that the oxidation at the nitrogen makes the sulfur moiety of VX a slightly better leaving group.

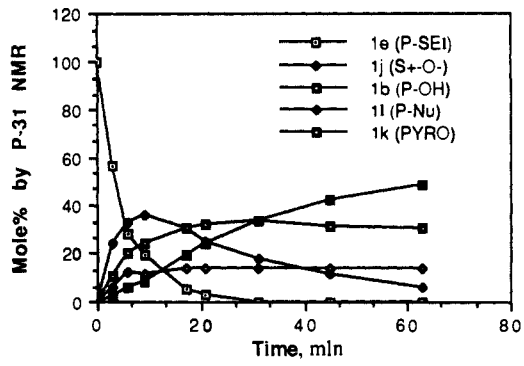
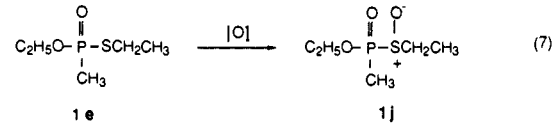



**Figure 2.** Oxidation of **1e** by excess *m*-CPBA in *tert*-butyl alcohol at 19 °C.

two competing rate processes by which **1g** could decompose. After a few hours, $^{13}C$ NMR indicated that **2c** decomposed presumably via further oxidation of the *N*-oxide.[9]

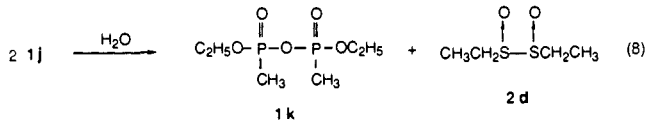
The relative oxidation reactivities of the N and S sites in VX can thus be drawn from the above results: (A) Oxidation of the sulfur atom occurred only after the amino nitrogen was oxidized to the *N*-oxide; and (B) further oxidation of the *N*-oxide by the excess oxidant occurred only after the sulfur was oxidized to the sulfonyl state. The lower basicity of the sulfur relative to the nitrogen is probably a result of electron delocalization to the phosphoryl oxygen.[14] Consistent results were obtained from the hydrolysis studies of VX reported previously.[4] As shown in eq 2, **3a** is the stable dimer of the diisopropylethyleneimmonium ion, which must have been present as a hydrolysis intermediate. This transient cyclic immonium ion is formed by the participation of the nitrogen as an internal nucleophile to break the S–C bond in VX. However, the formation of an ethylenesulfonium ion[15] via the participation of the sulfur in the breaking of the C–N bond has not been detected in the hydrolysis of VX.

**2. Oxidation of the Thiolo Sulfur.** In a mixture of 0.03 M **1e** and 0.24 M *m*-CPBA in pure *tert*-butyl alcohol, the oxidation of the sulfur and the subsequent cleavage of the P–S bond were further examined. As shown in Figure 2, **1e** was first oxidized to a stable intermediate, **1j**. Based on the NMR parameters (see Table 2A), the structure of **1j** is proposed in eq 7 and is consistent



(7)

with the oxidation product of a thioate reported previously by Fukuto and co-workers.[6] In the presence of an excellent sulfinyl leaving group, **1j** further reacted according to eqs 8–10 to form,



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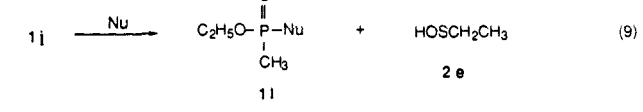

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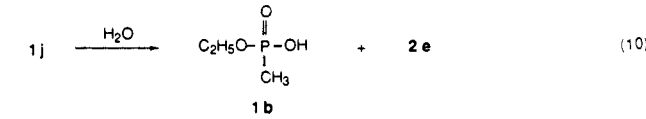


(10)

(14) Almasi, L. In *Sulfur in Organic and Inorganic Chemistry*; Senning, A., Ed.; Marcel Dekker, Inc.: New York, 1971; Vol. 1, Chapter 4.

(15) Yang, Y.-C.; Szafraniec, L. L.; Beaudry, W. T.; Ward, J. R. *J. Org. Chem.* **1988**, *53*, 3293–3297.

respectively, three products: **1k**, **1l**, and **1b**. While both **1k** and **1b** were positively identified, the structure of **1l** as detected at $\delta$ 26.5 in the $^{31}P$ spectrum was not confirmed. **1l** may be the product of **1j** with any one of the following possible nucleophiles (Nu in eq 9) present: *m*-chlorobenzoate, *m*-chloroperoxybenzoate, or an impurity in the oxidant. However, the fast isomerization of **1j** to the phosphonyloxysulfenate and the subsequent oxidation to the corresponding sulfonate cannot be ruled out.[5] Note that the ethylsulfenic acid product (**2e**) proposed in both eqs 9 and 10 was not detected. Instead, **2f** was the only product from oxidation of the sulfur in **1e** (see eq 11). In fact, competition between **2e**



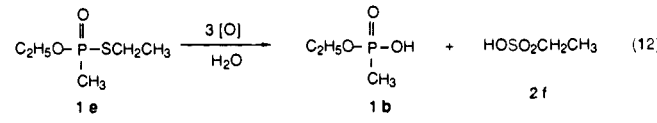
(11)

and the substrate, **1e**, for *m*-CPBA was observed: 3 mol of active oxygen was required to react with 1 mol of **1e**, indicating that the reaction between *m*-CPBA and **2e** was so fast that **2e** was oxidized to **2f** as soon as it was formed.

The sulfur in the VX *N*-oxide was oxidized by excess *m*-CPBA in a similar manner. In pure *tert*-butyl alcohol, five phosphorus-containing compounds were produced. The major product was **1b** since a trace amount of water was apparently present in the solvent. A significant amount of the pyrophosphonate **1k** was also formed. Of the other three compounds, one appears to be the sulfoxide or sulfonate ($\delta$ 26.5) of **1g** and the other two ($\delta$ 28.6 and 39.0) appear to be further displacement products of the sulfoxide, which can react with any nucleophiles present in the system.

**Formation of the Pyrophosphonate in the Absence of Water.** The pyrophosphonate **1k** is an important product since it is toxic (see Table I) and a major degradation product in neat VX as well as in solutions of VX in organic solvents.[16] As shown in Figure 2, the rate of production of **1k** was initially slow but increased as the concentration of **1b** began to decrease. This indicates that **1k** was produced after sufficient amounts of both **1j** and **1b** were present. Consequently, **1k** may also be produced from the reaction of **1b** with another molecule of VX or **1e**. Since the toxicity of **1k** is significant, a large amount of a nucleophile or water is required to react with **1j** in order to achieve detoxification. This subsequent displacement reaction must compete effectively with the formation of **1k**.

**Hydrolysis of the Sulfoxide Intermediate.** In an aqueous solution of 50 vol % *tert*-butyl alcohol, **1e** reacted quickly with the *m*-CPBA to produce **1b** and ethylsulfonic acid (**2f**) in a single step (equation 12). In the presence of water, the sulfoxide intermediate, **1j**, was



(12)

too short-lived to be detected by $^{31}P$ NMR; hydrolysis must have occurred as soon as the sulfur was oxidized. The observed first-order rate constant for eq 12 was determined in three *tert*-butyl alcohol–water mixtures in the presence of 20 times excess *m*-CPBA (0.44 M [O]). The half-lives were 1.0, 1.6 and 2.1 min, respectively, in *tert*-butyl alcohol containing 20, 25 and 10 vol % water. The small change in the above rates demonstrates that as long as a sufficient amount of water is present, the subsequent hydrolysis step is much faster than the oxidation step. Since the sulfoxide intermediate is polar, the measured rate decreases slightly as the polarity of the solvent decreases. In addition, it should be noted that the sulfur in **1e** is more reactive than the sulfur in VX. The oxidation rate of **1e** in 50 vol % *tert*-butyl alcohol was 5 times faster than that of the sulfur in the *N*-oxide of VX.

The identification of **1j**, or its reactive equivalent, the absence of hydrolytic reactivity for **1e**, and the fast oxidations of both VX and **1e** in aqueous solutions have made it possible to conclude that hydrolysis of both VX and **1e** occur only after the sulfur is oxidized. The alternate mechanism, which assumes oxidation of the

(16) D'Agostino, P. A.; Provost, L. R.; Visentini, J. *J. Chromatgr.* **1987**, *402*, 221–232.

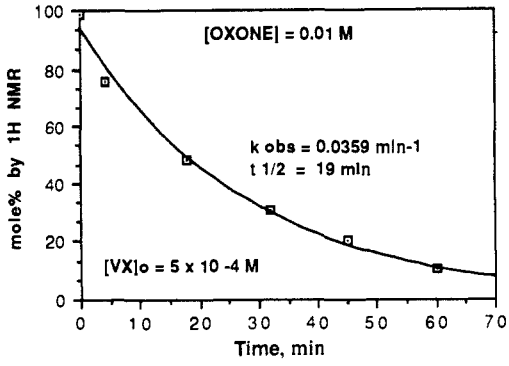
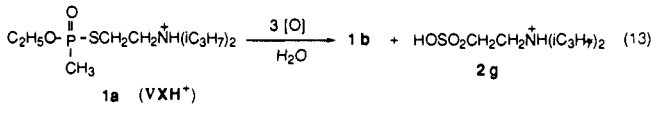



**Figure 3.** Observed first-order rate for the oxidation of VX by excess Oxone in $D_2O$ at 19 °C.

sulfur is preceded by hydrolysis at the P–S bond, is very unlikely.

**3. Oxidative Detoxification by Peroxides.** The reaction of both VX and **1e** with *tert*-butyl hydroperoxide (*t*-BuOOH) was monitored for a 24-h period in three solvent systems: *tert*-butyl alcohol, water, and 50 vol % *tert*-butyl alcohol–water. The only reaction detected was that of VX in pure water: VX hydrolyzed via the same parallel reaction paths as in eqs 1–3, but at a slightly faster rate. This small rate enhancement may be attributed to the subsequent oxidation of the sulfide hydrolysis products. However, neither oxidation nor hydrolysis occurred for **1e**. In a separate experiment, hydrogen peroxide was found to react with VX slowly. At room temperature in a mixture of 0.02 M VX and 0.85 M $H_2O_2$ in 90 vol % 2-propanol, compounds **1g**, **1f**, as well as **1b** were detected by $^{31}P$ NMR after ~18 h. The weak reactivity of the above oxidants is not surprising since even thioethers can only be oxidized very slowly by excess amounts of peroxides.[9] It is therefore concluded that peroxides, in general, cannot be used to detoxify the phosphonothiolates at ambient temperatures, unless perhaps metal catalysts are used.[17]

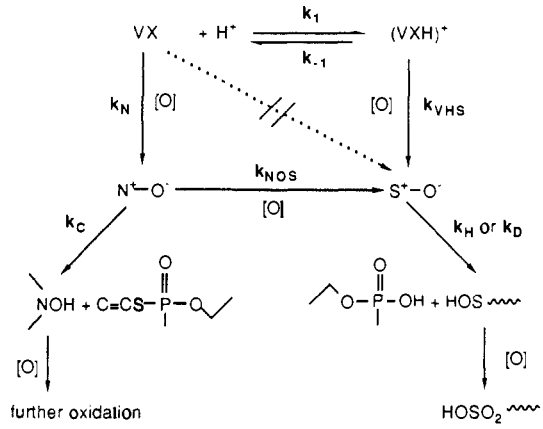
**4. Oxidation in Acidic Solutions.** VX reacted with Oxone ($2KHSO_5$–$K_2SO_4$–$KHSO_4$) quickly in pure water to form the phosphonic acid **1b** and sulfonic acid **2g** via exclusive P–S bond cleavage. Only 2 mol of Oxone containing 3 equiv of active oxygen were required to oxidize 1 mol of VX. Neither the VX *N*-oxide nor any other intermediates were detected during the course of the reaction. In the presence of 15 mol excess of Oxone, $^{13}C$ NMR showed that **2g** remained unchanged, and the nitrogen was not oxidized even after 24 h.[18] The single oxidation step shown in eq 13 appears to be due to the fact that the nitrogen is strongly protonated in the Oxone solution, which has a pH of 2.3 at 20 °C.



(13)

The curve in Figure 3 represents the fitted first-order rate constant for the oxidation of VX by excess Oxone ([O] = 0.017 M) in $D_2O$. This rate, with a half-life of 19 min, is fast enough for detoxifying VX at practical concentrations (e.g., 0.1 M), particularly since VX dissolves quickly in the acidic Oxone solution. In a less polar 50 vol % *tert*-butyl alcohol solution, the oxidation rate decreased. In addition to the major products **1b** and **2g**, ~2% **1g** was produced. The protonation of the nitrogen is apparently not as complete in 50% *tert*-butyl alcohol as in pure water. The oxidation of **1e** follows the same stoichiometry as in eq 12. The oxidation half-life in the presence of excess Oxone

**Scheme I.** Proposed Mechanism of VX Oxidation




(0.017 M [O]) is 4.8 min in $D_2O$, ~4 times faster than that of VX. (The *m*-CPBA, as discussed previously, also oxidized the sulfur in **1e** faster than that in the VX *N*-oxide.) This lower reactivity may be attributed to the steric effect of the amino group in VX since the sulfur in VX is expected to be more basic than that in **1e** (which does not hydrolyze). Similar to VX, the oxidation rate of **1e** was also slower in a less polar, 50 vol % *tert*-butyl alcohol solution. It is proposed that the transition state for oxidation is a sulfonium cation resulting from a single-electron transfer from the sulfur to the peroxygen of the peroxysulfate anion. The ions probably exist as an ion pair, which is less stable in less polar solutions.[19]

To verify the hypothesis that the nitrogen, once protonated, would not be oxidized, a reaction mixture of 0.01 M VX, 0.05 M HCl, and 0.04 M *m*-CPBA (0.032 M [O]) in 50 vol % *tert*-butyl alcohol was examined. No chlorophosphonate was detected as a reaction product or intermediate. More than 80% of the VX was oxidized directly to **1b** and **2g** according to eq 13 in less than 30 min. About 20% of the VX was not protonated and was oxidized at the nitrogen first. In contrast, as demonstrated in Figure 1 previously, all of the VX was oxidized to the *N*-oxide in the same solvent in the absence of any HCl. Furthermore, the overall reaction rate was faster in the presence of HCl than in a neutral solution. It is possible that the oxidation intermediate was more stable when both the phosphoryl and the sulfinyl oxygens were protonated. It is also possible that the peroxygen in the *m*-CPBA was more reactive since it was more electrophilic in an acidic solution (e.g., acid catalysis).[9]

**5. Multiple Paths of VX Oxidation.** Based on the discussions above, the mechanism of VX oxidation by a reactive peroxygen compound is proposed in Scheme I. In a neutral organic or neutral aqueous solution, VX is oxidized at the nitrogen first to form an *N*-oxide ($k_N$). The *N*-oxide is stable in aqueous solutions but decomposes in both protic and aprotic organic solvents by a Cope reaction ($k_C$). In aqueous solvents, the sulfur in the *N*-oxide molecule can be further oxidized by excess oxidant to a sulfoxide intermediate, which hydrolyzes immediately at the P–S bond ($k_H$). The rate of oxidation at the sulfur ($k_{NOS}$) is smaller than $k_N$. In acidic solution, VX is converted to an ammonium salt ($VXH^+$) and can only be oxidized at the sulfur. The acid oxidation path, $k_{VHS}$, is faster than the neutral oxidation path, $k_{NOS}$. In a less polar, acidic solution, a significant amount of unprotonated VX exists, and the nitrogen can be oxidized. The equilibrium between VX and $VXH^+$ ($k_1$ and $k_{-1}$; with a $pK_a$ of 8.6 at 25 °C in pure water)[20] is affected by the polarity of the solvent system, which controls the oxidation mechanism and products.

In the two extreme cases, organic solvents promote the reactions in the direction of $k_{-1}$, $k_N$, and $k_C$; whereas aqueous acidic solutions promote the reactions in the direction of $k_1$, $k_{VHS}$, and $k_D$ (the rate of the displacement reaction at the P–S bond after sulfur is

(17) The peroxides can be catalyzed by metal ions and metal complexes via the formation of a metal–oxo intermediate. (a) For oxidation of sulfides in apolar solvents, see: Campestrinni, S.; Conte, V.; Di Furia, F.; Modena, G.; Bortolini, O. *J. Org. Chem.* **1988**, *53*, 5721–5724, and references therein. (b) For oxidation of amines, see: Lindsey-Smith, J. R.; Mortimer, D. N. *J. Chem. Soc., Chem. Commun.* **1985**, 64–65.

(18) In the final acidic reaction mixture, **1b** hydrolyzed further to the nontoxic methylphosphonic acid (**1m**; see Table III) and ethanol, presumably via the acceleration of protonation.

(19) Professor Clifford A. Bunton, University of California at Santa Barbara, private communications.

(20) The $pK_a$ of VX was reported in: Epstein, J.; Kamiski, J. J.; Enever, R.; Sowa, J.; Higuchi, T. *J. Org. Chem.* **1978**, *43*, 2816.

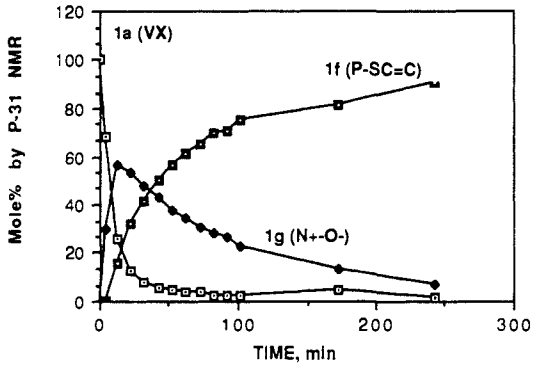
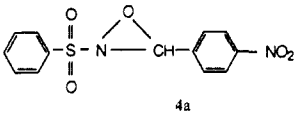



**Figure 4.** Oxidation of 0.02 M VX by 0.04 M **4a** in $CDCl_3$ at 19 °C.

oxidized). In both cases, the fast, secondary oxidation of the sulfide and amine products competes with VX for the oxidant. No direct oxidation of the sulfur in VX was observed before the nitrogen was oxidized or protonated. For a peroxygen compound, at least, the rate constant $k_S$ as represented by the dotted arrow in Scheme I does not exist.

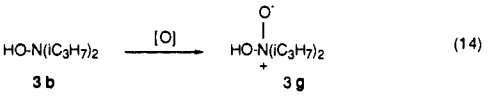
**6. Comparison with the Oxidation by *N*-Sulfonyloxaziridine.** In a series of recent publications,[11] the *N*-sulfonyloxaziridines such as **4a** were found effective in oxidizing a bivalent sulfur to the



**4a**

sulfoxide in organic solvents. It is our attempt to determine if the sulfur in VX could be oxidized by **4a** selectively and if the oxidation mechanism was different from the peroxyacids discussed above. Instead of *tert*-butyl alcohol, $CDCl_3$ was used as the solvent because **4a** is only sparingly soluble in *tert*-butyl alcohol. Similar to the oxidation by the *m*-CPBA discussed previously, VX was oxidized to **1g**, which subsequently decomposed to **1f** (see eqs 4 and 5). **4a** was reduced to an imine (**4b**), which hydrolyzed slowly to a sulfonamide (**4c**), and a benzaldehyde (**4d**) as a result of a trace amount of water in the $CDCl_3$ solvent (see Table IIB). The $^{31}P$ NMR profile of a reaction mixture containing 2 mol of **4a**/mol of VX is illustrated in Figure 4.

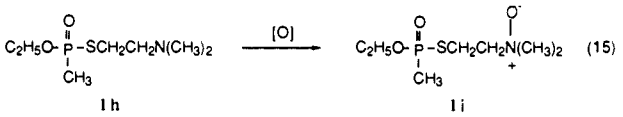
**Secondary Oxidation of the Hydroxylamine Product.** An oxidation stoichiometry different from that of the *m*-CPBA was observed, however. Two moles of **4a** was required to react with 1 mol of VX. Apparently, as VX was being oxidized, the hydroxylamine was produced at a comparable rate from the decomposition of the *N*-oxide **1g** and was able to compete with the VX for the oxidant (see eq 14). Only 1 equiv of *m*-CPBA was



**3b** **3g** (14)

required per mole of VX because the oxidation was faster and the Cope reaction was slower in *tert*-butyl alcohol. Thus, all of the oxidant was consumed by the VX before any of the hydroxylamine could be produced.

The effect of secondary oxidations on reaction stoichiometry was further examined by using a close derivative of VX, *O*-ethyl *S*-[2-(dimethylamino)ethyl] methylphosphonothiolate as the substrate (**1h**; see Table I for its toxicity). As shown in eq 15,



**1h** **1i** (15)

**1h** reacted instantaneously with 1 mol of **4a** to form 1 mol of the *N*-oxide **1i**, which was stable in $CDCl_3$ for at least 24 h. No Cope reaction occurred during this period. After 24 h, **1i** began to hydrolyze slowly and small amounts of both **1b** and the pyrophosphonate **1k** were identified by $^{31}P$ NMR. A comparison of the oxidation of **1h** with that of VX indicates that both the formation and the decomposition of the *N*-oxide are sterically controlled. **1i** forms at a faster rate but does not decompose by a Cope reaction. For the same reason, the smaller model compound, diisopropylmethylamine (**3c**), was oxidized instantaneously by both **4a** and *m*-CPBA to the *N*-oxide, which was stable even under GC/MS conditions (see the Experimental Section). Therefore, the hydroxylamine product (**3b**; see eq 14) must also oxidize at a faster rate than VX.

**Table I.** Toxicities of VX and Related Compounds[22]

| compd | $LD_{50}$, mg/kg rabbit I.V. | rabbit P.C. | mouse I.V. |
|---|---|---|---|
| VX, **1a** | 0.008 | 0.028 | 0.014 |
| **1d** | 0.017 | | |
| **1e** | 3.5 | 7.1 | 10.0 |
| **1h** | 0.014 | 0.16 | |
| **1k** | 0.089 | 7.1 | |

In the presence of 0.1 M **4a** at 10 mol excess, the half-life for the nitrogen oxidation in $CDCl_3$ was 4.1 min. Under identical conditions, VX was oxidized by *m*-CPBA to the *N*-oxide in less than 1 min. Instead of reacting as a selective oxidant for the bivalent sulfur, **4a** still oxidizes the nitrogen of VX first. This again demonstrates that the nitrogen in VX is a stronger nucleophile than the sulfur since the reaction mechanism of **4a** has been determined to be purely $S_N2$.[11] The rate of the decomposition of **1g** was independent of the oxidant concentration and had an approximate decomposition half-life of 28 min ($k_C$) in $CDCl_3$. Thus, the *N*-oxide is less stable in the aprotic $CDCl_3$ than in the protic *tert*-butyl alcohol solvent in which, as reported above, the decomposition half-life of the *N*-oxide was ~2 h. **1f** was not further oxidized by excess **4a** for at least 24 h.

**1e** reacted very slowly with **4a** in $CDCl_3$. After 22 h, only 36% of **1e** was converted to the pyrophosphonate **1k**. Since the $CDCl_3$ solvent is relatively inert, **1k** was found as the only displacement product from the sulfoxide **1j**. In a separate experiment, **1e** was mixed with excess *m*-CPBA in *tert*-butyl alcohol, which had been dried over molecular sieves. Different from the reaction profile shown previously in Figure 2, only small amounts of the four products **1b**, **1j**, **1k**, and **1l** were detected after 2 h.[21] Therefore, the observed rate of oxidation was significantly reduced in the absence of water.

It has been demonstrated that once the thiolo sulfur is oxidized the phosphonothiolate is activated. The ester becomes a reactive substrate in the presence of a good leaving group for displacement reactions. Although the chemical reactivities of these toxic esters can seldom be applied to their biological reactions, we would like to suggest that this is how VX becomes activated at the active sites of the enzymes and acts as an effective phosphorylating agent. In a recent study of the mechanism for acetylcholinesterase inhibition by *O,S*-dimethyl phosphoramidothioate ester,[6] the authors also suggested that the *S*-oxide of the ester was the metabolic-activated intermediate responsible for the observed high inhibitory potency.

## Summary

In VX, the amino nitrogen is more basic and oxidatively more reactive with a peroxygen compound than the thiolo sulfur, which oxidizes at a slower rate than that in **1e** as a result of the steric amino group. The sulfur oxidation in both VX and **1e** is accelerated by an increase in solvent polarity and an increase in the rate of the subsequent displacement reaction. In aqueous acidic solutions, the protonated nitrogen is resistant to oxidation; while sulfur oxidation is favored since the reaction intermediate is believed to be more stable when the sulfinyl oxygen is protonated. In apolar solvents, decomposition of both the VX *N*-oxide via a

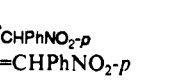
(21) As observed by Casida and co-workers (see ref 5), it was possible for **1j** to isomerize to a sulfenate ester, Me(OEt)P(O)(OSEt). The sulfenate ester could then be quickly oxidized to the sulfonate, $Me(OEt)P(O)(OSO_2Et)$, as the final stable product. This mechanism is being investigated in dry $CDCl_3$ in our laboratory.

**Table II**

(A) Representative NMR Parameters of Organophosphorus Compounds Identified

| compound/solvent | $^{31}$P, ppm | $^{13}$C,[a] ppm |
|---|---|---|
| VX, **1a**/water | 61.7 | $CH_3P$: 17.6 ($J$ = 107); $CH_3$: 15.1 ($J$ = 6); $(CH_3)_2$: 15.9, 17.6; $SCH_2$: 25.3 ($J$ = 2.8); $NCH_2$: 47.3; NCH: 55.1, 55.2; $OCH_2$: 63.4 ($J$ = 7.3) |
| **1a**/*tert*-butyl alcohol | 55.4 | |
| **1a**/$CDCl_3$ | 57.0 | |
| **1b**/water | 30.2 | $CH_3P$: 10.5 ($J$ = 135); $CH_3$: 15.4 ($J$ = 6); $OCH_2$: 61.0 ($J$ = 5.3) |
| **1c**/water | 76.4 | $CH_3P$: 26.2 ($J$ = 102); $CH_3$: 19.0 ($J$ = 7); $OCH_2$: 64.2 ($J$ = 5.5) |
| **1d**/water | 43.4 | $CH_3P$: 20.5 ($J$ = 108); $(CH_3)_2$: 16.4, 18.2; $SCH_2$: 26.2; $NCH_2$: 48.8; NCH: 55.1 |
| **1e**/water | 63.4 | $CH_3P$: 17.6 ($J$ = 107); $CH_3$: 15.5 ($J$ = 6); 15.8 ($J$ = 7); $OCH_2$: 63.1 ($J$ = 7.3); $SCH_2$: 26.2 ($J$ = 3) |
| **1e**/*tert*-butyl alcohol | 53.9 | |
| **1e**/$CDCl_3$ | 54.3 | |
| **1f**/*tert*-butyl alcohol | 51.8 | $CH_3P$: 18.8 ($J$ = 111); $CH_3$: 15.9 ($J$ = 6.8); $OCH_2$: 61.8 ($J$ = 7.2); $CH_2$: 122.2 ($J$ = 9.7); SCH: 124.6 ($J$ = 4.3) |
| **1f**/$CDCl_3$ | 53.6 | |
| **1g**/*tert*-butyl alcohol and water | 59.1 | $CH_3P$: 18.8 ($J$ = 110); $CH_3$: 15.6 ($J$ = 6.6); $(CH_3)_2$: 16.2, 16.5; CH: 67.4; $SCH_2$: 23.5; $OCH_2$: 62.6 ($J$ = 7.5); $N(O)CH_2$: 58.4 ($J \sim 2$) |
| **1g**/$CDCl_3$ | 56.0 | |
| **1h**/$CDCl_3$ | 56.8 | |
| **1i**/$CDCl_3$ | 56.1 | |
| **1j**/*tert*-butyl alcohol | 26.8 | $CH_3P$: 12.8 ($J$ = 143); $CH_3CO$: 16.0 ($J$ = 6.8); $CH_3CS$: 8.2; $OCH_2$: 64.0 ($J$ = 7.8); $SCH_2$: 48.4 |
| **1k**/*tert*-butyl alcohol | 23.4 | $CH_3P$: 12.8 ($J$ = 150); $CH_3$: 16.4; $OCH_2$: 63.0 |

(B) Representative $^{13}$C NMR Parameters of Organosulfur and/or Organonitrogen Compounds Identified

| | compound | solvent | $^{13}$C, ppm |
|---|---|---|---|
| **2a** | $HSC_2H_4N(i\text{-}Pr)_2$ | water | $(CH_3)_2$: 19.1; $SCH_2$: 23.4; $NCH_2$: 51.1; CH: 54.6 |
| **2b** | $(C_2H_4N(i\text{-}Pr)_2)_2S_2$ | water | $(CH_3)_2$: 20.0; $SCH_2$: 36.3; $NCH_2$: 48.0; CH: 57.6 |
| **2g** | $HOSO_2C_2H_4N^+H(i\text{-}Pr)_2$ | water | $(CH_3)_2$: 16.1, 17.5; $SCH_2$: 42.0; $NCH_2$: 46.4; CH: 54.9 |
| **2f** | $HOSO_2C_2H_5$ | water | $CH_3$: 8.5; $CH_2$: 45.5 |
| **3b** | $HON(i\text{-}Pr)_2$ | *tert*-butyl alcohol | $(CH_3)_2$: 17.1; NCH: 55.5 |
| **3c** | $MeN(i\text{-}Pr)_2$ | *tert*-butyl alcohol | $(CH_3)_2$: 18.4; $NCH_3$: 30.5; NCH: 52.6 |
| **3e** | $MeN^+O^-(i\text{-}Pr)_2$ | *tert*-butyl alcohol | $(CH_3)_2$: 16.7, 17.2; $NCH_3$: 44.8; NCH: 66.1 |
| **3d** | $H(HO)N(i\text{-}Pr)\cdot(COOH)_2$ | *t*-BuOH-$H_2O$ | $(CH_3)_2$: 16.6; CH: 53.9; C(O): 171.5 |
| **3f** | $H(HO)N^+O^-(i\text{-}Pr)\cdot(COOH)_2$ | *t*-BuOH-$H_2O$ | $(CH_3)_2$: 20.1; CH: 63.8; C(O): 171.5 |
| **4a** |  | $CDCl_3$ | CH: 74.6; Ph's (CH): 123.9 (2), 129.4 (4), 129.6 (2), 135.4; Ph's(C): 134.2, 137.2, 149.8 |
| **4b** | $PhSO_2N{=}CHPhNO_2\text{-}p$ | $CDCl_3$ | CH: 167.9; Ph's (CH): 124.2 (2), 132.0 (2), 128.3 (2), 129.4 (2); 134.2; Ph's(C): 137.2, 137.3, 151.2 |
| **4c** | $PhSO_2NH_2$ | $CDCl_3$ | Cl: 140.0; C2,6: 126.3; C3,5: 129.0; C4: 132.6 |
| **4d** | $O{=}CHPhNO_2\text{-}p$ | $CDCl_3$ | Cl: 142.2; C2,6: 130.4; C3,5: 124.3; C4: 151.2; C(O): 190.3 |

[a] $J$ values in hertz.

Cope reaction and the sulfoxide intermediate to a pyrophosphonate occur. Most of these decomposition products are toxic substances. The study has led to the design of effective detoxification systems by controlling the solvent properties, so that the sulfur in VX is oxidized selectively and quickly, the consumption of oxidant by secondary oxidations is kept at a minimum, and all of the reaction products are nontoxic.

## Experimental Section

**1. Materials. CAUTION!** Most of the organophosphorus substrates, products, and reaction intermediates described in this study are extremely toxic! Toxicities of some of these compounds are listed in Table I.[22] Note that **1e** is still quite toxic, although it is significantly less toxic than the rest of the compounds listed. One should not attempt to synthesize or work with these compounds unless proper training and adequate laboratory facilities have been acquired. The thiolate esters, VX, **1e**, and **1h** were prepared in-house and were greater than 95% pure by NMR and GC analysis.

The Oxone and the *m*-CPBA were technical grade products from Aldrich and were used as received. The active oxygen equivalent was determined by titration against a standard solution of 0.1008 M sodium thiosulfate with KI as the indicator. The Oxone was titrated in water, and the *m*-CPBA in isopropyl alcohol. Both samples were titrated in duplicate. The average oxidation equivalents were determined to be 1.74 per mol of Oxone and 0.83 per mol of *m*-CPBA. The *N*-sulfonyloxaziridine **4a** was obtained from Dr. Franklin A. Davis of Drexel University. The *tert*-butyl hydroperoxide was an anhydrous 3 M solution in toluene obtained from Fluka. *tert*-Butyl alcohol, obtained from Fisher Scientific, was freshly distilled and stored over molecular sieves. Both of the deuterated solvents, chloroform-$d_1$ (99.8 atom % D, MSD Isotopes), and deuterium oxide (99.8 atom % D, Stohler Isotope Chemicals), were used as received. Deionized distilled water was used for solvent preparations.

**2. NMR Experiments. A. Instrumentation.** The NMR spectra were obtained with either a Varian XL-200 or a Varian VXR-400S FT NMR system. The spectra were recorded at probe temperature (18–21 °C) in an unlocked mode. $^{31}$P spectra were recorded at 81 (XL-200) or 162 MHz (VXR-400S) by using a 247 ppm sweep width, a 33° pulse width, an acquisition time of 0.8 s, a pulse delay of 2.5 s, and gated WALTZ decoupling. Typically, 16–32 transients were required for each spectrum. Quantitative data were obtained by digital integration of the peak areas and are of ±3% accuracy. The peaks were referenced to external 85% phosphoric acid, and the chemical shift values are reproducible to ±0.1 ppm. The $^{13}$C spectra were recorded at 50 (XL-200) or 100 MHz (VXR-400S) with a sweep width of 250 ppm, a 42° pulse width, an acquisition time of 1.0 s, a pulse delay of 2.5–3.0 s, and full proton WALTZ decoupling. The peaks were referenced to an external sample of tetramethylsilane in chloroform, and the chemical shift values are reproducible to ±0.1 ppm. Representative NMR shift values of compounds investigated are summarized in Table IIA,B.

**B. $^{13}$C NMR Identification of the *N*-Oxides.** A sample of diisopropylmethylamine (**3c**), which was prepared in-house, was dissolved in *tert*-butyl alcohol and the $^{13}$C NMR spectrum obtained. The chemical shifts listed in Table IIB were consistent with the structure of the compound. Less than an equivalent amount of *m*-CPBA was added to the sample to produce the *N*-oxide product **3e**, the presence of which was confirmed by CI mass spectrometry (see Table III). The $^{13}$C NMR parameters of the *N*-oxide **3e** shown in Table IIB demonstrate that a carbon attached to a nitrogen will shift downfield ca. 13–14 ppm when the nitrogen is oxidized. To identify the *N*-oxide of a hydroxylamine, a

(22) Dr. H. S. Aaron and Mr. L. J. Szafraniec, CRDEC, private communications.

Table III. GC/MS-CI Identification of Oxidation Products

| compd | MW | $m/z^a$ |
|---|---|---|
| **1a** | 267 | 128, 268, 114, 252 |
| **1e** | 168 | 169, 141, 197, 209 |
| **1f** | 166 | 167, 139, 195, 123 |
| **1b** | 124 | 125, 97, 153, 165 |
| **1k** | 230 | 231, 259, 127, 203 |
| **1m** | 96 | 97, 111, 125, 137 |
| **2a** | 161 | 162, 128, 114, 89 |
| **2b** | 320 | 321, 160, 114, 128, 193 |
| **2f** | 110 | 111, 139 |
| **2g** | 209 | 210, 238, 250 |
| **3b** | 117 | 102, 116, 118 |
| **3e** | 131 | 132, 116, 72, 100, 263 |
| **4b** | 290 | 291, 331 |
| **4c** | 157 | 158, 141, 198 |
| **4d** | 151 | 152, 122, 180, 192 |

[a] In decreasing intensities.

sample of *N*-isopropylhydroxylamine oxalate (**3d**; Fluka Chemical, >98% pure) was dissolved in a 50 vol % *tert*-butyl alcohol solution, and the $^{13}C$ NMR spectrum was run to obtain reference chemical shift values (see Table IIB). An equal molar amount of *m*-CPBA was added to the solution. The nitrogen was oxidized immediately to the hydroxylamine *N*-oxide (**3f**). Consistent with the previous results, this caused the $\alpha$ carbon to shift downfield ca. 10 ppm (see Table IIB). Decomposition of **3f** occurred almost immediately; after a few hours, only $(CH_3)_2CH$-N=O ($^{13}C$ NMR: $\delta$ 18.0 and 60.3) and $(CH_3)_2C$=NOH ($^{13}C$ NMR: $\delta$ 15.0, 21.3, and 157.1) were observed in solution.

**C. Procedure for Kinetic Studies by $^{31}P$ NMR.** A weighed amount of the substrate (**1a**, **1e**, or **1h**) was placed into a new 5-mm-o.d. Pyrex NMR tube. The appropriate amount of oxidant was weighed into a separate glass vial and dissolved in the appropriate solvent. An aliquot of the oxidizing solution was then pipeted into the NMR tube; the tube was quickly capped, wrapped with Parafilm, and shaken to ensure complete mixing of the reactants. The NMR tube was placed in the spectrometer, and spectra were recorded periodically. The substrate concentrations were typically 0.01-0.05 M. The estimated error in the rate determinations is ±3-5%.

**D. Procedure for the Rate Determination in Dilute Solutions by $^1H$ NMR.** Observed first-order rates were determined for VX and **1e** in the presence of excess Oxone (0.1 or 0.17 M [O]) in $D_2O$ by $^1H$ NMR. The substrate concentration was 0.0005 M, and the spectrum was recorded periodically using the VXR-400S FT NMR at 18.5 °C. The sweep width was narrowed to 1.6 ppm to observe only the methyl region. Sixty-four transients were accumulated for each spectrum by using a 90° pulse width and a repetition rate of 3.74 s. The progress of the reaction was monitored by following the disappearance of the $CH_3P$ doublet of the reactant and the appearance of the $CH_3P$ resonances from the phosphonic acid product **1b**. The resonances were expanded and digitally integrated to obtain the peak areas.

**3. Gas Chromatography/Mass Spectrometry Identification.** Gas chromatography/mass spectrometry (GC/MS) and direct exposure probe (DEP) mass spectrometry were used to assist and confirm the NMR identification of the oxidation products. Spectra were obtained on a Finnigan Model 5100 GC/MS in the chemical ionization mode. Methane (0.6 Torr internal source pressure) was used as the reagent gas. The source temperature was 100 °C. Both phosphonic and sulfonic acids and other ionic products could be detected with the DEP, which was ramped from 0 to 1 A at 200 mA/s. The identification of volatile organic products was made by extracting these products from the aqueous reaction mixtures into methylene chloride and characterizing the extract by GC/MS.

The instrument was equipped with a 25 m × 0.25 mm i.d. fused-silica GB-1 capillary column (Foxboro/Analabs, North Haven, CT). The injection port temperature was 210 °C, and the oven was programmed from 60 to 270 °C at 10 °C/min. A 0.01-$\mu$L aliquot of sample was injected with a split ratio of 50:1. The mass range was scanned from 60 to 450 amu at a rate of 1 scan/s. Spectral assignments were obtained by comparison to reference spectra in an existing in-house library and on the basis of characteristic fragmentation patterns. The CI mass spectra of the major products are listed in Table III.

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# An Approach to the Design of Molecular Solids. The Ureylenedicarboxylic Acids

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**Abstract:** The crystal structures of a series of ureylenedicarboxylic acids have been determined as part of a project directed toward the design of molecular solids. The ureylenedicarboxylic acids were chosen for study because they were predicted to form a two-dimensional hydrogen-bonded network. This two-dimensional network is the result of two orthogonal linear arrays of self-complementary hydrogen-bonded functionalities, the dicarboxylic acids and N,N'-disubstituted ureas, being present in the same molecule. The simplest molecules of the series, 2,2'-ureylenediacetic acid (**1**), 3,3'-ureylenedipropionic acid (**2**), and 4,4'-ureylenedibutyric acid (**3**) as well as the simplest ureylene derived from a dipeptide, *N,N'*-carbonylbisglycylglycine (**4**) were synthesized and studied by using X-ray crystallographic techniques. Each molecule was found to crystallize to give the predicted solid-state structure. Two compounds, related to compound **3**, were also studied. the methyl ester of **3**, dimethyl 4,4'-ureylenedibutyrate (**5**), crystallizes to give a one dimensional network based only upon hydrogen bonds between the urea functionalities. The thiourea analogue of **3**, 4,4'-thioureylenedibutyric acid (**6**) forms a network based upon carboxylic acid hydrogen bonds, but there is no linear alignment of the thiourea functionality presumably due to the lower energy of hydrogen bonds to sulfur.

The design of molecular solids is a worthy but elusive goal.[1] In order for a molecular solid to exibit a particular solid-state phenomena, such as electrical conductivity, nonlinear optical behavior, or solid state polymerization, the composite molecules must possess both the requisite molecular structure *and* molecular orientation in the solid state. Chemical synthesis is employed for the preparation of a given molecular structure. However, the ability to control or even predict solid-state structure is a very difficult problem with few useful solutions.

Dipolar interactions play an important role organizing molecules in the solid state. Among these dipolar interactions, the hydrogen

(1) The number of reports in both the scientific and popular literature are an indication of the awareness that is developing with respect to new materials. For example, a recent issue of *Science* was entirely devoted to this subject (*Science* **1990**, *247*, 608).

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