Chemical Detoxification of Nerve Agent VX

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Received March 16, 1998

Nerve Agents and Chemical Weapon Stockpiles

The chemical warfare (CW) nerve agents, commonly known as nerve gases, are not gases but polar organic liquids at ambient conditions. Most of these nerve agents are P(V) organophosphorus esters that are similar in structure to insecticides and can irreversibly react with the enzyme acetylcholinesterase (AChE), inhibiting its control over the central nervous system.[1−3] The G-type nerve agents (Chart 1) were first developed in Germany in the 1930s but were not used in World War II. In the 1950s, the V-type nerve agents (Chart 1), which are more toxic and more persistent than the G-agents, were developed. Currently, there are two known V-agent stockpiles: VX (*S*-2-(diisopropylamino)ethyl *O*-ethyl methylphosphonothioate), with thousands of tons in the United States, and an analogue and isomer, R-VX (Russian-VX, *S*-2-(diethylamino)ethyl *O*-isobutyl methylphosphonothioate), in Russia.[4,5] Based on a recent study,[6] the decontamination chemistries of these two agents are very similar.

In addition to VX, the United States also stockpiled thousands of tons of GB (Sarin) and sulfur mustard ($S(CH_2CH_2Cl)_2$), a blister agent that attacks tissues.[7] These stockpiles are being destroyed by incineration, although alternative technologies including chemical neutralization are also being considered for specific storage sites.[8] In 1997, the United States ratified the Chemical Weapons Convention (CWC) Treaty, which bans the possession and use of chemical weapons, controls the chemicals that are used to produce them, and requires total destruction of any CW stockpiles.[9] The safety and environmental impact of the destruction process are of great concern to the general public.

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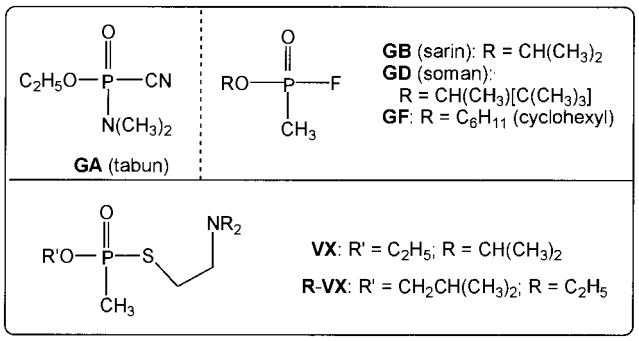
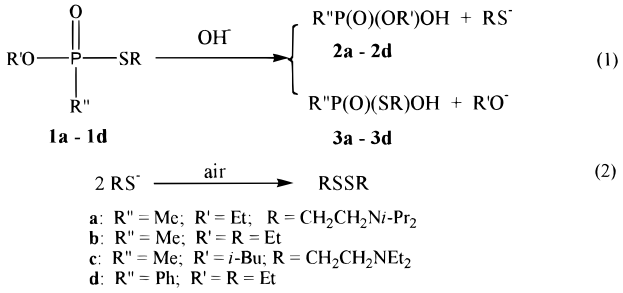
Chart 1. Structures of Chemical Warfare Nerve Agents



Chemical Detoxification

A convenient and effective method to detoxify small amounts of agent, agent-contaminated surfaces, or containers is to use a liquid solution containing excess reactants to chemically convert the agent to significantly less toxic products rapidly at ambient conditions. For example, at room temperature in mildly basic solutions (e.g., aqueous sodium carbonate), GB dissolves and reacts with OH^- rapidly to form nontoxic NaF and the sodium salt of isopropyl methylphosphonate,[10] but the hydrolysis of V-agents is not as effective (eqs 1 and 2). VX has limited



solubility in basic solutions, reacts with OH^- slowly ($t_{1/2}$ = 31 min at 0.1 M NaOH and 22 °C; k_{OH} of VX ≃ $10^{-3}k_{OH}$ of GB),[10,11] and gives a stable but highly toxic thioic acid byproduct, **3a**. (Note that, in this paper, the same compound number is assigned to both the acid and its conjugate base, although, depending on the pH of the solution, they may not coexist.) Instead, VX is frequently detoxified with copious amounts of aqueous bleach (containing NaOCl or $Ca(OCl)_2$). The reaction proceeds vigorously and rapidly via oxidation-promoted hydrolysis at the P−S bond with simultaneous oxidation at the tertiary amino moiety.[12,13] As a result, up to 20 mol of active chlorine is consumed per mole of VX. If insufficient bleach is used, residual VX and **3a**, produced from hydrolysis, can be found in the final mixture after the active chlorine has been consumed. Because of the more complex reactivity of VX, its chemistry was not as extensively studied as that of the G-agents.

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Published on Web 11/04/1998

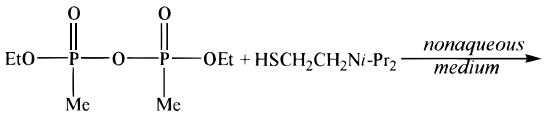
Decontamination, Neutralization, and Destruction

The above reactive detoxification approach falls under the general category of solution decontamination,[12] and similar chemical conversions can be accomplished in a chemical reactor (e.g., a continuously stirred tank reactor, CSTR) using large quantities of agents and reactants under controlled temperature, pressure, agitation, and flow rates. This chemical process is also called neutralization aimed at the disposal of bulk agents. Reactants and solvents suitable for formulating a decontamination system may not be appropriate for neutralization because of different goals. For example, the ability to rapidly react with all types of agents, ease of application, and material compatibility are important factors for decontamination, whereas process control, safety, and the nature of the reactor effluent, including spent reagents, products, byproducts, and the fate of agent impurities, are areas of emphasis in neutralization. Once the agent is detoxified in the reactor, the product effluent can be safely treated for final discharge to the environment. The optimum posttreatment process (e.g., chemical oxidation, supercritical water oxidation (SCWO), or biodegradation) is dependent on the nature of the reactor effluent.[8] As substances cannot be destroyed but can be transformed, "destruction" of VX is its irreversible conversion into compounds that can be safely disposed to land, water, and air.

Properties and Analysis

VX can be prepared by reacting QL (MeP(OEt)(OCH_2-$CH_2N(i\text{-}Pr)_2$; a P(III) ester) with elemental sulfur to form a P(V) *O*-alkyl phosphonothioate intermediate, which isomerizes to VX (i.e., the binary method).[14] Pure VX has a boiling point of 298 °C,[14] a liquid density of 1.0083 g/mL (25 °C),[15] and a viscosity of 9.96 cP (25 °C).[16] The solubility of VX in water is 4.8 wt % at 21.5 °C; the solubility of water in VX is 15 wt % at 23 °C; and these solubilities increase as temperature decreases, giving a U-shaped temperature vs composition phase diagram.[17] The LD_{50} values (50% of the lethal dose) of VX are 0.008 mg/kg (intravenous, rabbit) and 0.028 mg/kg (percutaneous, rabbit), and one drop is enough to kill a human being.[15,18] At 20 °C, the vapor pressure of VX is 7.0×10^{-4} mmHg and is much lower than that of GB (2.10 mmHg).[15] Because of its low volatility and relative stability toward spontaneous hydrolysis (50% degradation in 78 h at 22 °C in unbuffered water), VX is a persistent nerve agent. Under long-term storage in the presence of a trace amount of water, VX slowly hydrolyzes to produce a small amount of **2a**, which reacts with the bulk VX to give the toxic diphosphonate **4a** (the reverse of eq 3), a major impurity from degradation.[19−21] Depending on the synthesis, there are numerous impurities in VX present in minute quantities, and some of the phosphorus-containing impurities are quite toxic.[16,21] If the chemical reaction is specific to VX and the toxic impurities do not react, they may become a safety concern in downstream processing.

Like most organic compounds, VX and its neutralized products may be analyzed by gas chromatography (GC) or liquid chromatography (LC) coupled with mass spectrometry (MS)[20,21] and by multinuclear (^1H, ^{13}C, and ^{31}P) nuclear magnetic resonance (NMR) spectroscopy.[22] A combination of these methods is usually required in order to characterize one sample. For some aqueous samples, extracting the VX into organic solvent for GC/MS analysis has proven difficult, since the pH of the sample matrix must be adjusted to above the pK_a of VX (8.6 at 25 °C),[11] which may affect the chemistry of the sample system. Extracting from aqueous matrix and concentrating both impurities and reaction products into an organic solvent can favor re-formation of VX in trace amounts, especially at the elevated temperatures encountered in the GC injection port (e.g., eq 3). In addition, many of the



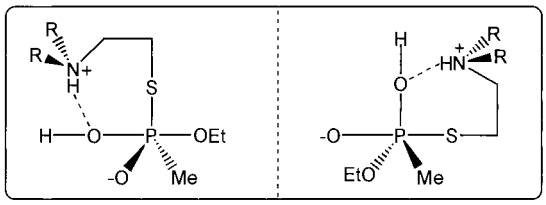
4a VX + MeP(O)(OEt)OH (3)

reaction products are ionic (e.g., **2a** and RS^-) and which do not readily chromatograph in the gas phase without derivatization, but the chemistry involved in derivatization could also cause re-formation.[16] On the other hand, NMR can be used to monitor most VX reactions occurring in a single phase without having to manipulate the highly toxic samples. NMR can also be performed on concentrated samples typical of neutralization reactions, allowing the observation of interactions between VX and products, intermediates, or byproducts which may not exist in the dilute GLC samples.

Chemical Reactions

VX typically reacts with anionic nucleophiles at phosphorus, and, depending on the pK_a of the nucleophile, the O-alkyl and/or the S-alkyl groups are displaced.[23] VX also reacts with oxidants at the electron-rich S and N (deprotonated) centers,[24] although weaker oxidants (e.g., H_2O_2 or ozone)[25] only oxidize at the amino group but not at the thiolo sulfur, and detoxification is not achieved when the P−S bond is not cleaved. In addition, like most organic molecules, VX also reacts with free radicals or radical anions such as $OH^\bullet$ or $SO_4^{\bullet -}$ which attack most covalent bonds. These reactions are particularly desirable for agent disposal because they offer one-step treatment, producing inorganic final products (e.g., PO_4^{3-}, SO_4^{2-}, and CO_2) which can be directly discharged.[27] Because of the nonselective nature of these reactants, they usually react with all types of agents, agent degradation products, impurities, and additives. However, these reactions generally suffer from small throughput, low efficiency, and high cost. More complicated process control may be necessary to handle short-lived free radicals, oxidants, and gaseous effluents. Most of the reactions that may be useful for neutralization were summarized in a recent

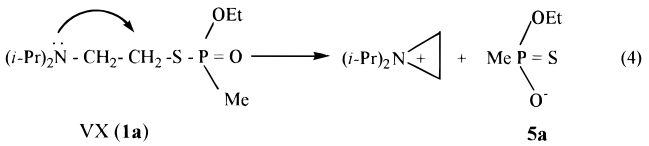
Chart 2. Proposed Schemes for Intramolecular Amino Group-Catalyzed Hydrolysis



publication.[26] A discussion on recent research in the detoxification chemistry of VX follows.

(1) Reaction with H_2O or OH^-. Neutral to Weakly Basic Solutions. The kinetics and mechanism of the hydrolysis of VX are dependent on pH and temperature. At 23 °C in unbuffered water, 0.01 M VX (pK_a = 8.6) dissolves and coexists with its protonated species, VXH^+. The hydrolysis is slow, with a half-life of 60 h based on the initial observed rate constant, k_{obs}, which decreases as pH decreases from 10.2 initially to 7.5 after 8 days. All of the products are initially soluble in water (eq 1), except that the thiolate anion slowly reacts with oxygen to form the disulfide (eq 2), appearing as oily droplets floating on top of the solution. In addition to the intermolecular reaction with OH^- at phosphorus (eq 1; k_{OH}), the reaction is catalyzed intramolecularly (k_i) by the amino group, with either the O-ethyl or the S-alkyl group departing from the apical position opposite to the attacking H_2O molecule or the anionic phosphoryl oxygen (Chart 2, note that some of the charges and bonds are partially developed).[28,29] The amino group is not an intermolecular catalyst because, at a constant pH, measured rates are independent of the initial concentration of VX. In contrast, **1b** (eq 1) did not react with H_2O over 7 months at 23 °C, and little hydrolysis was observed for VX in acidic solutions (e.g., from pH 2 to 2 M H_2SO_4). At 23 °C, measured rates vs pH (up to pH 13) show $k_{obs} = k_i + k_{OH}[OH^-]$ with $k_{OH} = 5.19 \times 10^{-3}$ M^{-1} s^{-1} for VX, and $k_{obs} = k_{OH}[OH^-]$ with $k_{OH} = 3.35 \times 10^{-3}$ M^{-1} s^{-1} for **1b**. **1b** is an excellent model compound for comparative studies to isolate the intramolecular effect of the amino group in VX.

Nitrogen-Assisted C−S Bond Cleavage at Elevated Temperatures. In weakly basic solution, the neighboring amino group (deprotonated) can assist in the cleavage of the C−S bond to produce the nontoxic thioic acid (**5a**) and a cyclic ethyleneiminium ion (eq 4). This S_N1-type



(4)

displacement at the C−S bond is slow at ambient temperatures ($k_o = 4.6 \times 10^{-7}$ s^{-1} at 23 °C) but becomes more competitive as temperature increases (E_a = 25.7 kcal/mol).[30] For example, a solution of 1.0 wt % VX (~0.04 M) was heated at 87 °C for 2 h. The observed rate, corresponding to an initial half-life of 32 min, decreased with time as the solution became more acidic. After 1 h, 36% VX remained (pH 8.0); after 2 h, 22% VX remained (pH 7.5), and **2a**, **3a**, and **5a** at a mole ratio of 40/20/40 as measured by ^{31}P NMR were produced. Both **2a** and **3a** were mainly produced from the amino group-catalyzed hydrolysis as described above, and **5a** from eq 4 was a major product. Since residual VXH^+ and the toxic **3a** may be present in the final effluent, decontamination of VX by hot water may not be effective. For R-VX (**1c**), the same reaction path also occurs, but **5c** is produced more slowly than **5a**,[6] probably because the smaller cyclic diethyl ethyleneiminium ion is less favored relative to the bulkier diisopropyl analogue.

Table 1. Product Ratio from the Reaction of OH^- and MeP(O)(OEt)(SEt) (1b)[a]

temp, °C	[**1b**], M	base	solute/solvent	PS/PO or **2b**/**3b**[b]
23	0.001	0.01 M NaOH	H_2O	76/24
	0.01	0.1−0.5 M NaOH	H_2O/D_2O	76/24
	0.01	0.1 M NaOH	25 vol % *t*-BuOH	76/24
			25 vol % CH_3CN	76/24
	0.10	1.0 M NaOH	H_2O	72/28
	0.005	2.0 M NaOH	H_2O	66/34
	0.005	3.0 M NaOH	H_2O	60/40
	0.005	3.0 M Me_4NOH	H_2O	66/34
	0.005	4.0 M NaOH	H_2O	59/41
	0.005	4.0 M LiOH	H_2O	61/38
	0.005	0.1 M NaOH	1.0 M NaF/H_2O	77/23
	0.005	0.5 M NaOH	3.5 M $NaCl/H_2O$	78/22
	0.005	0.5 M NaOH	3.5 M $NaNO_3/H_2O$	79/21
	0.005	0.5 M NaOH	1.3 M Na_2SO_4/H_2O	79/21
50	0.005	4.0 M NaOH	H_2O	61/39
75	0.005	4.0 M NaOH	H_2O	67/33
90	0.005	4.0 M NaOH	H_2O	74/26
90	0.005	0.5 M NaOH	H_2O	84/16
90	0.005	0.1 M NaOH	H_2O	84/16

[a] All of the samples are of a single liquid phase. [b] In mol/mol based on 100 mol of **1b**; measured by ^{31}P NMR with a maximum error of 2 mol %.

Intermolecular Reaction with OH^-. In basic solutions at pH >12, the major reaction is attack of OH^- on phosphorus to give **2** and **3** simultanously (eq 1). Detailed ^{31}P and ^{13}C NMR analyses of **1a,b,d** (including PhP(O)(^{18}-OEt)(SEt)) in 0.1 and 4.0 M NaOH in $H_2{}^{18}O$ demonstrated that **3** was produced from P−O, not O−C, bond cleavage (i.e., OH^- attacks at phosphorus, not at the ethoxy carbon).[30] In solutions of up to 1.0 M NaOH, k_{obs} increases at more than first-order in $[OH^-]$, probably because decreased water activity makes the OH^- a more reactive nucleophile. At 23 °C, the P−S/P−O cleavage ratio is constant from 0.01 to 0.5 M NaOH (i.e., 88/12 for VX (**1a**); 76/24 for **1b** (Table 1); and 86/14 for **1d**), but this ratio decreases consistently in still higher [NaOH] (e.g., to 73/27 for VX; 59/41 for **1b** (Table 1); and 66/34 for **1d** in 4 M NaOH). As shown in Table 1 for **1b**, ionic strength, the nature of cations and anions present, and solvent properties have little effect on product selectivity, and it is not obvious why P−O bond cleavage is favored at very high [NaOH]. Within experimental error, measured rates of VX at pH 12 give the same E_a of 14.5 kcal/mol for both P−S and P−O cleavages.[29] However, based on the product analyses of both VX and **1b** (Table 1), **2a** clearly

increases with temperature, indicating E_a for P−S cleavage is actually larger than that for P−O cleavage.

At room temperature, both products **2a** and **3a** are stable, but, at elevated temperatures, **3a** hydrolyzes at moderate rates (i.e., $t_{1/2}$ = 35 min at 75 °C in 2.0 M NaOH), and **2a** hydrolyzes much slower (i.e., k_{OH}(**3**)/k_{OH}(**2**) ≈ 140 at 90 °C).[29] These results show that VX can be completely detoxified in concentrated NaOH at elevated temperatures because any toxic **3a** produced is subsequently converted to the nontoxic $MePO_3^{2-}$ and RS^-. These findings form the basis of the VX neutralization process at 90 °C being developed by the U.S. Army.[8] Note that, in the neutralization reactor at high temperatures with high loadings of VX and NaOH, VX is present as a separate organic phase with hydrolysis occurring rapidly at the interface. The disulfide product (eq 2) eventually forms a small top organic phase in the final product, although the reactor is operated under nitrogen. It is important to ensure adequate mixing in the reactor so that VX is not trapped in this organic phase. Thermal decomposition of RS^- to *i*-Pr_2NH, $RSCH_2CH_2SH$ and other products was also observed at 90 °C.

Autocatalytic Hydrolysis. An unusual interaction between VX or R-VX and water occurs in an equimolar nonaqueous mixture of V-agent and water (water/V-agent = 0.07 g/g). The V-agent is completely hydrolyzed within 1−2 months at room temperature to **2a** and RS^- via P−S cleavage.[16] This slow reaction is initiated by attack of deprotonated **2a** on protonated VX (VXH^+) to produce the diphosphonate intermediate **4a**, which rapidly hydrolyzes in the presence of a stoichiometric amount of water. About 0.2−0.4 mol % of a toxic impurity, $MeP(O)(SCH_2CH_2N$*i*-$Pr_2)_2$, also reacts via the same mechanism to give **3a**, which is stable in the final reaction mixture. It is speculated that this small amount of **3a** may contribute to the toxicity of the final product mixture.

(2) Reactions with H_2O_2. The reaction of VX with H_2O_2 is also dependent on pH. In mildly basic to basic solutions, VX reacts with the α nucleophile HO_2^- at a rate 40 times that of OH^- (i.e., $t_{1/2}$ = 45 s at 23 °C and 0.1 M HO_2^-), giving exclusive P−S cleavage, and this reaction mechanism was recently examined with molecular orbital calculations.[31] The reaction is nucleophilic substitution at phosphorus, followed by oxidation of the RS^- product to the disulfide (RSSR) and eventually to the sulfonate anion (RSO_3^-), which is soluble. The pK_a of H_2O_2 is 11.0 and is much smaller than that of HOEt (pK_a = 15.9), so HO_2^- does not displace the OEt group.[23] Excess H_2O_2 over OH^- is usually used to generate the HO_2^-, and most of the OH^- is consumed to deprotonate the H_2O_2. Any residual OH^- reacts with VX too slowly to compete with HO_2^-; therefore, **3a** is not produced. Similarly, the peroxy hydrolysis of 0.01 M VX is complete in less than 2 min at 23 °C in an aqueous solution of 0.5 M peroxycarbonate ($Na_2CO_3{\cdot}2H_2O_2$), a component used in commercial detergents. Other α nucleophiles such as iodosobenzoates and oximates also react with VX or VX analogues, giving exclusive P−S cleavage,[23] although more slowly than HO_2^-.

In weakly acidic H_2O_2, rapid intramolecular amino group-catalyzed HO_2^- substitution was observed. When 0.01 M VX was added to 14% H_2O_2 ([O] = 4 M; pH 4), the pH of the solution immediately increased to 8.0, and the VX began to react. This reaction was initially rapid ($t_{1/2}$ = 3.1 min at 24 °C based on initial rate), slowed as acidic products were produced, and eventually stopped at pH 4 and 47% VX after 1 h when the amino nitrogen in the remaining VX was protonated. In comparison, **1b** reacts very slowly in 14% H_2O_2 buffered at pH 8 because [HO_2^-] is small. In the presence of a polar organic solvent, H_2O_2 can oxidize the deprotonated nitrogen in VX, but no oxidation at the sulfur followed by P−S cleavage has been observed.

In strongly acidic H_2O_2 solutions (mixtures of H_2O_2 and up to 6 M H_2SO_4, HCl, or H_3PO_4), VX readily dissolves. The nitrogen is protonated and not oxidized. Reactive $H_3O_2^+$ is generated and oxidizes at sulfur, followed by hydrolysis to give **2a** and RSO_3H. This reaction is very similar to that of VX with peroxyacids to be discussed later.

(3) Reaction with Alkoxide Anions. Alkoxide anion (RO^-) in alcohol is a nonaqueous system for rapid dissolution and reaction of VX.[23] A simple alcohol and K or Na metal are usually mixed to prepare the alkoxide, whose reactivity increases as the size of the alkyl group increases. Diols (e.g., ethylene diglycol), ether alcohols (e.g., $CH_3OCH_2CH_2OH$ as used in a standard decontamination solution, DS2),[12] or amino alcohols (e.g., $HOCH_2CH_2NH_2$, monoethanolamine or MEA, a popular solvent and reactant for agent neutralization)[26] can also be used to generate the alkoxide ion, whose reactivity increases as the solvent is less protic. At 0.25 M CH_3O^- in methanol, VX reacts with $t_{1/2}$ = 15 min at 22 °C, giving the thiolate anion and the diester $CH_3P(O)(OCH_3)(OC_2H_5)$ as the major product. There is <5% displacement at the P−O bond, giving a thioate ester intermediate, $CH_3P(O)(OCH_3)(SR)$, which is similar to VX and rapidly reacts with another CH_3O^- to form $CH_3P(O)(OCH_3)_2$.[23] The observed rate for **1b** is proportional to [CH_3O^-]^2 but varies linearly with the Hammett's acidity function (H_M) of methoxide.[32] Given time (1−2 days), the diester products slowly hydrolyze to form phosphonate anions, **2a** and $CH_3P(O)(OCH_3)O^-$. Based on the nature of the intermediates and final products, the alkoxide reaction differs from those of solvated electrons which can be generated from mixing Na with ammonia or amines and can attack most carbon−heteroatom covalent bonds.[33]

When KOH or NaOH is used instead of alkali metals or when water is present in the solvent, OH^- forms and competes with RO^- in reacting with VX. This reaction will produce the toxic **3a**, which is persistent because **3a** reacts with CH_3O^- very slowly ($t_{1/2}$ = 140 h at 0.30 M CH_3O^-, 22 °C). In alcohol alone, and similar to Chart 2, the amino group in VX may also act as a general base and catalyze the alkoxide substitution at phosphorus intramolecularly.

(4) Oxidation by Peroxyacids. VX is rapidly oxidized by strong peroxyacids such as the peroxymonopersulfate in OXONE ($KHSO_4{\cdot}K_2SO_4{\cdot}2KHSO_5$), magnesium monoperoxyphthalate (MMPP), peroxyacetic acid, and *m*-chlo-

Table 2. Examples of VX Simulants

chemical name	structure
diethyl methylphosphonate (DEMP)	$CH_3P(O)(OC_2H_5)_2$
tri-*n*-butyl phosphate	$P(O)(O\text{-}n\text{-}C_4H_9)_3$
O,*S*-diethyl methylphosphonothioate	$CH_3P(O)(OC_2H_5)(SC_2H_5)$ (**1b**)
O,S-diethyl phenylphosphonothioate	$C_6H_5P(O)(OC_2H_5)(SC_2H_5)$ (**1d**)
thiophenyl diphenylphosphinate	$(C_6H_5)_2P(O)(SC_6H_5)$
thiophenyl diethyl phosphate	$(C_2H_5O)_2P(O)(SC_6H_5)$
p-nitrophenyl diethyl phosphate (PNPDEP or paraoxon)	$(C_2H_5O)_2P(O)(OC_6H_4NO_2\text{-}p)$
p-nitrophenyl diethylphosphorothioate (parathion)[a]	$(C_2H_5O)_2P(S)(OC_6H_4NO_2\text{-}p)$
S-[2-(ethylthio)ethyl] *O*,*O*-diethylphosphorothioate (Demeton S)[a]	$(CH_3CH_2O)_2P(O)(SCH_2CH_2SCH_2CH_3)$
S-[2-(ethylthio)ethyl] *O*,*O*-dimethylphosphorothioate (Demeton-S-Methyl)[a]	$(CH_3O)_2P(O)(SCH_2CH_2SCH_2CH_3)$
S-(1,2-dicarbethoxylethyl) *O*,*O*-dimethyl dithiophosphate (malathion)[a]	$(CH_3O)_2P(S)(SCH(CH_2C(O)OC_2H_5)(C(O)OC_2H_5))$
S-phenyl *O*-ethyl ethylphosphonothioate (fonofos)	$(C_2H_5)P(S)(OC_2H_5)(SC_6H_5)$

[a] Insecticide.

roperoxybenzoic acid (m-CPBA) in aqueous or aqueous−polar organic solvents. The reaction is initiated by oxidation at the sulfur, an electrophilic attack, followed by hydrolysis at the P−S bond to produce **2a** and RSO_3H. VX is soluble in the $KHSO_4$ buffer (pH 1.9) of OXONE, and the amino nitrogen is not oxidized. However, the solubility of OXONE is limited, and the oxidant decomposes at pH above 5. MMPP and m-CPBA are more stable at higher pH, in which a fraction of the deprotonated amino nitrogen is oxidized and an additional oxygen is consumed.

The oxidation is strongly retarded by a decrease in solvent polarity, and this phenomenon was extensively investigated with model compounds.[34] As the sulfur is being oxidized, an ionic transition state develops and requires polar solvents to solvate and stabilize the charges. In nonaqueous solutions, the S-oxide was identified in model compounds, and its isomerization to RS−O−P(O), which rapidly oxidizes to $R-O_2S-O-P(O)$, was reported.[35,36] In organic solvents, as reported previously,[24] the S-oxide of VX or **1b** reacts with another substrate molecule to form toxic **4a** as the major product. The toxic *N*-oxide of VX also forms, and, depending on the polarity of the organic solvent, it may be a stable final product in more polar solvents (e.g., *t*-BuOH), or it may decompose in less polar solvents (e.g., $CHCl_3$) via the Cope reaction to give the toxic thioate, $MeP(O)(OEt)(SCH{=}CH_2)$.[24] Therefore, aqueous solutions *must* be used if VX is to be detoxified via oxidation by a peroxyacid.

Little reaction was detected between VX and peroxydisulfate anion ($S_2O_8^{2-}$) at room temperature. Addition of sulfuric acid to peroxydisulfate produces the monoperoxysulfate anion ($HOOSO_3^-$), which is the active component in OXONE and reacts with VX similarly.[26] At 22 °C, VX reacts with 7.8 M HNO_3 very slowly, giving final products **2a** and the sulfonic acid, and presumably the reaction is similar to that of the peroxyacid. However, the reaction may be autocatalytic because it is slower at the initial and final stages, with a maximum rate corresponding to a $t_{1/2}$ of 28 h.

(5) Catalytic Hydrolysis. Although iodosobenzoate (IBA) derivatives are excellent nucleophilic catalysts for the hydrolysis of GB and GD in weakly basic micelles,[37,38] they react stoichiometrically with **1d** (eq 1), because IBA is reduced by the RS^- leaving group.[38] Recently, an organophosphorus hydrolase (OPH) enzyme from *Pseudomonas diminuta* was demonstrated to cleave the P−S bond of both VX and R-VX, but the observed hydrolysis was very slow.[39,40] No transition metals or complexes have yet been reported to catalyze the hydrolysis of V-agents.

Related Compounds

Experiments with VX or R-VX can only be conducted by specially trained personnel in a limited number of laboratories approved for handling CW agents, but significant information can still be obtained from research with model compounds or simulants (Table 2). Most, if not all, of those simulants mimic only limited aspects of VX chemistry, and none of the compounds in Table 2 can simulate the unique intramolecular amino nitrogen effect in VX. In general, in substitution reactions, the phosphates and the O-alkyl thioates (containing P═S bond) react slower and the phosphinothioates (containing two C−P bonds) react faster than VX. In oxidation reactions, the P═S group oxidizes faster than the S-alkyl group, and those compounds that do not contain sulfur or nitrogen atoms do not react with any of the oxidants described above. Both **1b** (mildly toxic) and **1d** (nontoxic) have been used to simulate the intermolecular substitution and oxidation of VX.

Conclusion

The nerve agent VX can be chemically detoxified via two major classes of selective chemical reactions under ambient conditions—nucleophilic substitution with exclusive P−S bond cleavage (e.g., using aqueous peroxycarbonate) and hydrolysis initiated by oxidation at sulfur (e.g., using aqueous peroxymonopersulfate). In weakly basic solutions, where the intermolecular substitution at phosphorus is slow, the intramolecular amino group can participate as a nucleophile at carbon or as a general base catalyst for substitution at phosphorus. VX reacts with water or hydroxide with cleavage of both P−S and P−O bonds, and the thioic acid (**3a**) produced from P−O cleavage is almost as toxic as VX and is unreactive with anionic nucleophiles except under extreme conditions. But, **3a** oxidizes or hydrolyzes in acidic solutions more rapidly than VX.[41] Only limited success has been achieved with catalytic hydrolysis for VX. Most model compounds

do not adequately simulate the unique and versatile reactivities of VX, and one must be cautious in inferring simulant data to VX. A discussion on recent research in the reaction chemistry of VX has been presented in the hope that future studies will lead to better reaction systems to detoxify VX more effectively and more efficiently.

The author is grateful to Dr. Clifford A. Bunton at the University of California for helpful discussions; Linda L. Szafraniec and Lawrence R. Procell at the U.S. Army ERDEC for significant technical input; and Col. J. Girlando and Dr. J. Illinger at USARDSG-UK for management support during the preparation of the manuscript.

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AR970154S