Autocatalytic Hydrolysis of V-Type Nerve Agents

Yu-Chu Yang,* Linda L. Szafraniec, William T. Beaudry, Dennis K. Rohrbaugh,
Lawrence R. Procell, and John B. Samuel

Research and Technology Directorate, U.S. Army, Edgewood Research, Development, and Engineering Center (ERDEC), Aberdeen Proving Ground, Maryland 21010-5423

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Both V-type nerve agents MeP(O)(OR)($SCH_2CH_2NR'_2$), VX (R = C_2H_5; R′ = *i*-C_3H_7) and its isomeric analog RVX (the “Russian V-agent”, R = *i*-C_4H_9; R′ = C_2H_5), react slowly but completely with an equimolar amount of H_2O via exclusive P−S cleavage to produce the corresponding phosphonic acid (MeP(O)(OR)OH) and 2-aminoethanethiol ($HSCH_2CH_2NR'_2$). The reaction is believed to be initiated by nucleophilic attack of the deprotonated phosphonic acid on the protonated V-agent to produce a diphosphonate intermediate ($(MeP(O)(OR))_2O$) that rapidly hydrolyzes to regenerate the phosphonic acid. The autocatalytic ionic chain reaction is thus continued in the nearly nonaqueous reaction medium. The viscous final product mixture remains reactive toward freshly added trace amounts of the V-agent, giving the same final reaction half-life of 13−15 h at 23 °C. When water is insufficient and depleted, the diphosphonate intermediate accumulates and reacts with the aminoethanethiol to regenerate the V-agent. This autocatalytic hydrolysis process is not observed with a simpler phosphonothioate analog (MeP(O)(OC_2H_5)(SC_2H_5)), which suggests that the attack of the phosphonic acid on the V-agent is intramolecularly assisted by the protonated amino group.

Introduction

There has been a heightened interest in the chemistry of chemical warfare agents since the National Research Council recommended chemical neutralization as one of the potential alternative methods for the destruction of chemical weapons.[1] Of the known weaponized nerve agents, the relatively new V-type agents, methyl phosphonothioates (MeP(O)(OR)($SCH_2CH_2NR'_2$) are among the most toxic and persistent.[2,3] Thousands of tons of two isomeric V-agents have been declared as stockpiles in two countries—VX (**1**, R = Et; R′ = *i*-Pr) in the United States and RVX (“the Russian V-agent”, **2**, R = *i*-Bu; R′ = Et) in Russia.[4,5] These stockpiles are to be destroyed in the near future, and the safety as well as environmental impacts of the destruction process are of ultimate concern.[1] We present in the following an NMR study of the background chemistry of a simple neutralization approach—to detoxify the V-agents by adding about 7% water (equimolar) to the V-agent in a closed container. Our small-scale (up to 50 mL) experiments showed that in 30−60 days at room temperature, the V-agents were completely converted to less toxic products by a unique autocatalytic hydrolysis process.[6] Thus, any conceivable human or environmental exposures to these exceedingly lethal compounds during neutralization are minimal, and the total mass of the final neutralized product is only increased by less than 10% over the agent feed.

VX (*O*-ethyl *S*-(2-(diisopropylamino)ethyl) methylphosphonothioate, CAS No. 50782-69-0) has been known to slowly degrade in storage to ethyl methylphosphonic acid, 2-(diisopropylamino)ethanethiol, and the toxic *P,P′*-diethyl dimethyldiphosphonate (**1a**, **1d**, and **1c** in Scheme 1, respectively) in the presence of trace amounts of water.[7] The following short-term laboratory observation also confirmed this degradation. A freshly prepared 94.9% pure VX sample (feed 1, no inhibitor added, see the following discussion) was stored in a capped NMR tube placed in an oven at 35 °C and was analyzed by ^{31}P NMR once a week. After 3 weeks, the major degradation product **1c** increased from less than 0.6 to 2.6 area %; about 0.2 area % **1a** was also detected; and the purity of the VX decreased to 92.1%. In practice, 2−5% by weight of an inhibitor, diisopropyl- or dicyclohexylcarbodiimide (*i*-PrN=C=N*i*Pr (DICDI) or $C_6H_{11}N{=}C{=}NC_6H_{11}$(DCCDI)) was added to the stockpiled VX to retard the degradation. The inhibitor can react with H_2O, **1a**, and **1d** to form urea and thiourea (Table S-4, Supporting Information), so that further degradation of VX is prevented.[7]

It is conceivable that if a small but sufficient (i.e., stoichiometric) amount of water is deliberately added to VX, both VX and **1c** should continue to hydrolyze to completion giving only two nontoxic final products, **1a** and **1d**. It may be possible to develop a large-scale process that chemically neutralizes the V-agent stockpiles *in-situ* (i.e., inside the original container). Therefore, we have investigated the reaction of both VX and RVX (*O*-isobutyl *S*-(2-(diethylamino)ethyl) methylphosphonothioate, CAS No. 159939-87-4) with up to 10% water—an equimolar mixture gives H_2O/V-agent = 0.067 g/g. We have also studied a simple thioate analog, *O,S*-diethyl methylphosphonothioate (**3**, MeP(O)(OC_2H_5)(SC_2H_5)), under comparable reaction conditions to isolate the effect

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[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1996.

(1) Committee on Review and Evaluation of the Army Chemical Stockpile Disposal Program, National Research Council. *Recommendations for Disposal of Chemical Agents and Munitions*; National Academy Press: Washington, D. C., 1994.

(2) Yang, Y.-C.; Szafraniec, L. L.; Beaudry, W. T.; Rohrbaugh, D. K. *J. Am. Chem. Soc.* **1990**, *112,* 6621−6627.

(3) Yang, Y.-C.; Baker, J. A.; Ward, J. R. *Chem. Rev.* **1992**, *92,* 1729−1743.

(4) (a) Voronov, V.; Fedorov, L. Chemical Weapons or Chemical War? Moscow Khim. Zh. **1993**, July, No. 7, 66−70. (b) Beletskaya, I. P.; Novikov, S. S.; Chemical Weapons in Russia. *Vestn. Ross. Akad. Nauk* **1995**, *65*(2), 99−104.

(5) *Mendeleev Chemistry Journal* (*Zhurnal Ross. Khim. Ob-va im. D. I. Mendeleeva*); Allerton Press, New York, 1993; Vol. 38, No. 2.

(6) Yang, Y.-C. *Chem. Ind.* **1995**, No. 9, 334−337.

(7) The observed degradation did not result from air oxidation or from thermal decomposition as was verified by monitoring VX samples under both wet and dry nitrogen at 100 °C. See: Rohrbaugh, D. K.; et al. *Studies in Support of SUPLECAM II. 1. Thermal Decomposition of VX*, CRDEC-TR-88056, May 1988, Aberdeen Proving Ground, MD, unclassified report.

S0022-3263(96)01450-8

of the intramolecular amino group in the observed hydrolysis process.[8,9]

Typically, mixtures of VX−water and RVX−water were prepared as 0.7−1.5 mL size samples and monitored by ^{31}P NMR over weeks to months at 22−23 °C. A few larger size samples from 10 to 50 mL were also investigated. The results (rates and products) are highly reproducible. Most of the samples were not mixed to simulate a direct addition of water to the V-agent stored in a container. Mixing is usually unimportant for very slow reactions. Reported H_2O/V-agent weight ratios assumed 100% V-agent purity, whereas calculated mole ratios were based on agent purity as analyzed by ^{31}P NMR (Tables S-1−3, Supporting Information). Two grades of VX were used for sample preparations: 95% pure without any inhibitor and 91% pure with approximately 2% DICDI added (feeds 1 and 2 in Table S-1 (Supporting Information), respectively). The final products were further analyzed by ^{1}H and/or ^{13}C NMR and by GC/MS/CI with sample derivatization (Tables S-1−5, Supporting Information). Quantitative data are based on NMR results, whereas the GC/MS/CI identifications are used to confirm the NMR assignments (Table S-4, Supporting Information). Major findings on the fundamental chemistry of the hydrolysis process are reported below.

Results

(1) Reaction Rates and Products. Reaction Rate Profiles. When a small amount of distilled water was added to a large amount of VX (H_2O/VX = 0.07−0.10 g/g) at room temperature, the initial mixture appeared to be homogeneous,[10] but a small aqueous phase settled out in the bottom of the flask after a few hours (see Experimental and Table S-6 (Supporting Information) for a detailed investigation into this phase separation phenomenon). In spite of the phase separation, VX reacted slowly without any mixing to produce two major final products **1a** (δ_P 20.1) and **1d** in about 45−60 days. As shown in the reaction mixture (H_2O/VX = 0.06 g/g) in Figure 1, VX (feed 1) decreased while **1a** increased monotonically with reaction time, and up to 2 area % **1c** (δ_P 22.3; 22.5) was detected as a reaction intermediate. (Diphosphonates such as **1c** contains two asymmetric phosphorus atoms that give two closely spaced ^{31}P NMR resonances of equal intensities corresponding to the *d,l*- and the meso-isomer pairs). The initial data points in Figure 1 are based on analysis of the top phase (~90%), although the sample became one phase after 9−11 days when more than 50% of the VX had reacted. When ^{18}O water (75% ^{18}O) was used to prepare the VX−water mixture ($H_2{}^{18}O$/VX = 0.07 g/g), the same final products were formed in the final single-phase mixture, except that ^{18}O was found in both the intermediate **1c** (multiple ^{31}P NMR resonances; δ_P 22.23−22.35; 22.50−22.65) and the final product **1a** (δ_P 20.16; 20.14), indicating that water was indeed a reactant.

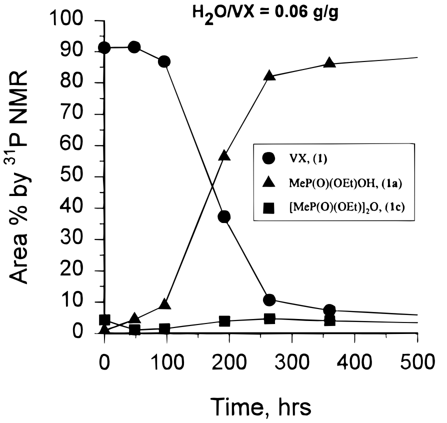

Figure 1. ^{31}P NMR monitoring of a VX−water mixture (6% water) at 23 °C.

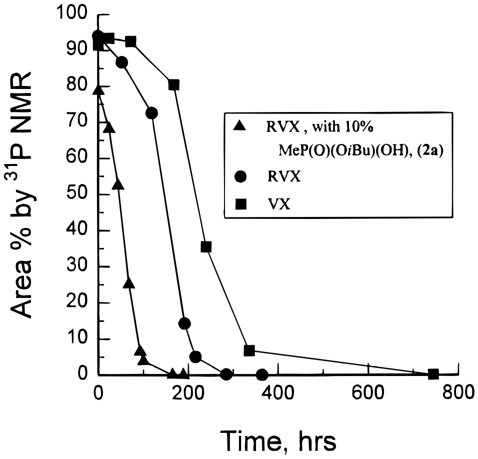

Figure 2. Degradation of V-agents with 8% H_2O at 23 °C.

RVX reacted in the same manner as VX to produce **2c** as the intermediate and **2a** (MeP(O)(O*i*Bu)OH) and **2d** (Scheme 1) as the final products with a similar reaction profile as shown in Figure 1 for VX. However, there is a major difference and advantage of this mixture (H_2O/RVX = 0.08 g/g)—it was homogeneous and remained a single phase throughout the reaction without any mixing. This resulted in a more rapid reaction of RVX than VX, particularly at the initial stage (Figure 2). However, both VX and RVX gave similar rate profiles composed of three distinct regions: a slow initial rate, a maximum rate, and a slow tailing rate region for the final 10% reaction. The half-lives of this final rate region were about 13 h for RVX and 15 h for VX (a single phase). As shown in Figure 2, when 10 wt % of pure **2a** was added to the initial RVX-water mixture to form a single-phase sytem, the initial rate of RVX was significantly accelerated, indicating **2a** could be a reactant or a catalyst.

Reactivity of V-Agent Spikes in the Final Mixtures. To determine if the reaction was complete, up to 96 h of ^{31}P NMR signal accumulations were performed on the final samples to detect any trace amounts of VX or RVX. In the final VX−water sample, seven small major peaks plus a few pairs of ^{13}C side bands in the VX region (δ_P 51−53) were detected with a total integrated area of less than 0.1%. A VX spike (δ_P 52.3) of about 1000 ppm was injected into the sample to ascertain if one of these peaks was indeed VX. The spike overlapped with one of the^{13}C side bands, but reacted (i.e., decreased with time) until the original spectrum was obtained. The half-life of the spike reaction was 15 h and was identical to the final reaction rate of the original VX−water

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[8] Leslie, D. R.; Pantelidis, S. *Aust. J. Chem.* **1994**, *47*, 545−559.

[9] Yang, Y.-C.; et al. Hydrolysis of VX: Activation Energies and Autocatalysis. In *Proceedings of the 1994 ERDEC Scientific Conference on Chemical Defense Research*, 14−18 Nov 1994, Aberdeen Proving Ground, MD, in press.

[10] The solubility of H_2O in VX is ca. 0.15 g/g at 25 °C; see: Coulter, P. B.; Callahan, J. J.; Link, R. S. *Physical Constants of Thirteen V-Agents*, CWLR 2346, Dec, 1959, Aberdeen Proving Ground, Maryland, unclassified report.

mixture. This spiking experiment proved unambiguously that VX was not present in the final product mixture. The detection limit in this sample matrix was 5 ppm. This NMR method was used for trace V-agent detection because it was discovered that GC/MS analyses on derivatized product samples could give a false-positive identification of VX at the ppm level (Experimental Section).

A similar spiking experiment was performed on the RVX−water final product. As shown in Figure S-1 (Supporting Information), the RVX spike of about 900 ppm (Figure S-1c, δ_P 54.7) did not overlap with any of the other peaks in this region of the original spectrum (Figure S-1a,b, δ_P 53.8−55.4). This spike reacted at the same final reaction rate as that of the original sample with a half-life of 13 h (Figure S-1d) until it was reduced to below the detection limit of 9 ppm, and the same original spectrum was obtained. Therefore, no RVX was present in the sample. The fact that these final mixtures remained reactive toward the V-agent spikes indicated that it was highly unlikely for any V-agent to be left in the final mixtures. For practical application, the inner surfaces of the V-agent container can be slowly decontaminated by this final liquid mixture stored in the container.

Composition of the Final Product. As shown in Tables S-1−5 (Supporting Information), the major components in the final samples were the phosphonic acid (MeP(O)(OR)OH (**a**), R = Et (**1a**) or *i*-Bu (**2a**), 92−97 area % by ^{31}P NMR analysis) and the aminoethanethiol ($HSCH_2CH_2NR'_2$ (**d**), R′ = *i*-Pr (**1d**) or Et (**2d**), 42−45 area % by ^{13}C NMR analysis), produced from P−S bond cleavage in the V-agents. Characteristic of the synthesis, VX contains numerous impurities present in trace amounts. Some of these impurities containing P−S (δ_P 49−62) and P=S (δ_P 65−86; 94−103) bonds were unreactive and remained in the final mixture (Table S-1, Supporting Information). However, the major impurity **1c** (up to 4 area % in feed 2) reacted rapidly before any detectable reaction of VX.

Cleavage at the P−O and C−S Bonds. Although two thioic acids, the toxic $MeP(O)(SCH_2CH_2NiPr_2)OH$ (**4**, 0.3 to 0.4 area % and the nontoxic MeP(S)(OEt)OH (0.4 to 1.3 area %) were detected in the final mixtures (Table S-1, Supporting Information) and could be from the hydrolysis at the P−O and C−S bonds of VX, but their small yields and lack of detectable trends suggested that they were produced from reactions of the impurities but not from VX itself. As an example, about 0.1−1.0 area % of the bis-diester impurity $MeP(O)(SCH_2CH_2NiPr_2)_2$ was present in VX and was found to react rapidly to produce **4**, which is a highly toxic product (LD_{50}-mouse: 0.017 mg/kg). This compound may have contributed to the measured toxicity of the final product mixture (LD_{50}-mouse: 8−15 mg/kg), which was 3 orders of magnitude lower than that of the VX feed (LD_{50}-mouse: 0.008−0.011 mg/kg). Consistently, in the RVX−water system, the corresponding thioic acid product $MeP(O)(SCH_2CH_2NEt_2)OH$ was not detected (detection limit: 20 ppm) because the corresponding diester $MeP(O)(SCH_2CH_2NEt_2)_2$ was not present in the RVX feed.

Stability of the Final Product. When the final VX−water mixture was diluted with an equivolume of water, the pH of the solution was 6.4−6.5 at 23 °C. In these neutral to weakly acidic final mixtures, **1a** is stable but **1d** slowly decomposed to *i*-Pr_2NH, *i*-$Pr_2NCH_2CH_2SCH_2CH_2SH$ (**1e**), and a number of the corresponding disulfides via air oxidation, [*i*-$Pr_2NCH_2CH_2S]_2$ (**1f**), *i*-$Pr_2NCH_2CH_2SSCH_2CH_2SCH_2CH_2N$-*i*-$Pr_2$ (**1g**), and (*i*-$Pr_2NCH_2CH_2SCH_2CH_2S)_2$ (**1h**). These secondary products were identified by GC/MS/CI and by ^{13}C NMR (Tables S-3 and S-5, Supporting Information). When the VX−water reaction (H_2O/VX = 0.10 g/g) was conducted at 90 °C, 98% of the initial VX reacted after only 6 h, and large amounts of the above secondary products (**1e**−**h**) were produced. However, neither VX nor **4** could be detected in the heated sample from possible reverse reaction paths involving **1a** and **1d**. To verify this observation, an equimolar mixture of $MeP(O)(OEt)_2$ and **1d** was prepared and heated at 90 °C for 4 h. No reaction of the diester or any VX reformation was detected by GC/MS/CI (detection limit: 0.01 area %). The *O*-ethyl leaving group in the diester was not displaced by **1d**. Relative to the more reactive diester, the phosphonic acid **1a** is even less likely to react with **1d** under similar conditions.

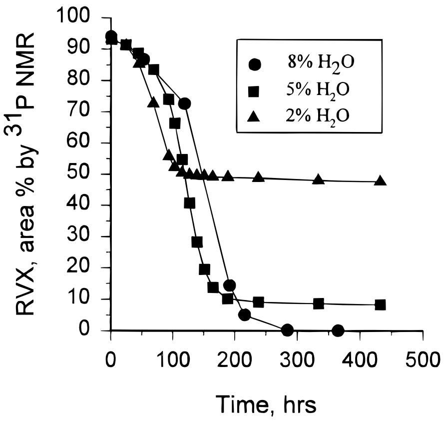

Figure 3. Degradation of RVX with various amounts of water at 23 °C.

Viscosity of the Final Mixture. The final reaction mixtures were distinctly more viscous (viscosity, η = 130 c.s. at 25 °C) than the initial mixture (η = 10.1 c.s. for VX at 25 °C). Furthermore, the viscosity of an equimolar mixture of pure **1a** (η = 48.3 c.s. at 25 °C) and **1d** (η = 1.8 c.s. at 25 °C) was 95.5 c.s. at 25 °C, more viscous than either of the pure components. A small decrease in the volume of the reaction mixture was observed at the end of the reaction (specific gravities of VX and the final product mixture at 25 °C were typically 1.01 and 1.03, respectively).

(2) Reactions with Varying Amounts of Water. Effect of Water on Rates and Products. In VX−water mixtures with less than equimolar amounts of water, both VX and **1c** were present in the final products. The accumulated amount of **1c** increased as the amount of added water decreased (see Experimental Section and Table S-6, Supporting Information). As illustrated in Figures 1 and 2 with 6 and 8% added water, respectively, the mixture with less water reacted faster initially but the reaction seemed to have stopped before reaching completion, whereas the mixture with excess water initially reacted slower but the reaction became faster at the final stage until all of the VX disappeared. The presence of water apparently reduced the reaction rate but was essential to drive the reaction to completion. Similarly, as shown in Figure 3 for the three RVX−water mixtures, the initial rates were faster in mixtures with less water. Whereas the reaction at 8% water reached completion, the reaction in 2 and 5% water (H_2O/VX =

Table 1. Reaction Half-Lives and Products of 1c in Aqueous and Organic Solutions at 23 °C[a,b]

solvent/solution	pH	product or product mole ratio	rate ratio (r_w/r_d)[c]	$t_{1/2}$, min
H_2O		**1a**		358[d]
0.10 M $KHSO_4$ in water	2.0	**1a**		238
0.01 M NaOH in water[e]	12.0	**1a**		<1
0.12 M Et_3N in water	12.0	**1a**		~0.7[f]
0.12 M Et_2NH in water	12.1	**1a**		<1
0.12 M **2d** in water	10.1	**1a**/V-type[g] = 72/28	0.79	42
1.0 M H_2O in **1a**		**1a**		96
0.1 M H_2O in **2d**[h]		**1a**/V-type[g] = 64/36	0.39	22
0.1 M H_2O in **1a** and **2d**[i]		**1a**/V-type[g] = 75/25	1.0	37
2.0 M H_2O in **1a** and **2d**[i]		**1a**/V-type[g] = 95/5	9.0	14
a final product mixture[j,k]		**1a**/VX = 98/2	24	20

[a] 0.01 M **1c** unless specified. [b] In organic solutions, 1.0 M H_2O is less than 2% H_2O by volume. [c] $r_w/r_d = (2 \times \mathbf{1a} - 1)/(2 - 2 \times \mathbf{1a})$; **1a** is expressed in mol %. [d] Based on the initial rate data. [e] 0.001 M **1c**. [f] Estimated at 40 s on the basis of one data point at 4 min after mixing. [g] The V-type product is $MeP(O)(OEt)(SCH_2CH_2NEt_2)$. [h] The added water was not completely miscible with **2d**, and the results may have large uncertainties. [i] **1a**/**2d** = 52/48 mol/mol. [j] 0.5% **1c**. [k] The initial composition of the reaction mixture was H_2O/VX = 0.10 g/g, reaction time was 60 days, and the reaction temperature was 23 °C. The final product sample contained 43.2% **1a**, 20.3% **1d**, and 11.9% *i*-Pr_2NH in mol % by ^{13}C NMR; the other minor components are mainly the degradation products of **1d**, i.e., **1e**−**h**.

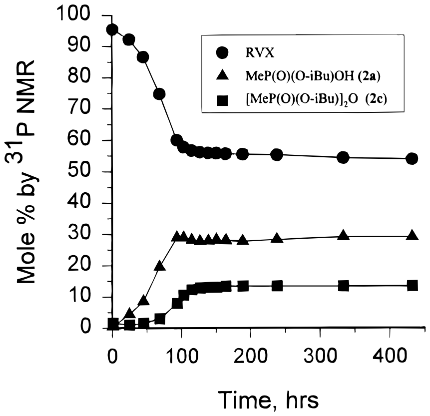

Figure 4. Reaction profile of RVX with 2% water at 23 °C.

0.32 and 0.80 mol/mol) stopped at about 50 and 90% RVX conversion, respectively. In the mixture with 2% water (Figure 4), the yield of **2a** was about 32 area % by ^{31}P NMR and was equivalent to the amount of water added. The diphosphonate **2c** (Scheme 1), which was likely produced from the reaction of RVX and **2a** (eq 1), was a

$$\mathrm{MeP(O)(OR)(SCH_2CH_2NR'_2)} + \mathrm{MeP(O)(OR)OH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{[MeP(O)(OR)]_2O} + \mathrm{HSCH_2CH_2NR'_2} \quad (1)$$

major final product in the 2% water mixture; a minor product in the 5% water mixture (Table S-7, Supporting Information) but was absent in the final mixture of 8% water. The final concentrations of the mixtures with 2 and 5% water were also analyzed by ^{13}C NMR and listed as samples 5 and 6 in Table S-7 (Supporting Information). It appears that if **2c** is present in the mixture, RVX will also be present; and vice versa.

Reverse Reactions in the Absence of Water. To determine if an equilibrium involving the reaction of **2c** and **2d** to regenerate RVX exists (eq 1), a nearly equimolar mixture of **2a**, **2c**, and **2d** was prepared (sample 4 in Table S-7, Supporting Information). After 24 h, about 9 mol % RVX was detected. Similarly, about 8 mol % VX was produced from a nearly equimolar mixture of **1a**, **1c**, and **1d** (Sample 3 in Table S-7, Supporting Information) in less than 18 h. This equilibrium for the reformation of V-agent is absent as long as a sufficient amount of water is present to react with **c** (eq 2) to eliminate **c** from the reaction mixture.

$$\mathrm{[MeP(O)(OR)]_2O} + \mathrm{H_2O} \xrightarrow{k_2} 2\ \mathrm{MeP(O)(OR)OH} \quad (2)$$

To further verify the reversible reactions shown in eq 1, two nearly equimolar mixtures of VX and **1a** (sample 1) and **1c** and **1d** (sample 2) were mixed and monitored by ^{31}P NMR until the composition in each mixture became constant. The final compositions of the two mixtures were analyzed by ^{13}C NMR and were the same, giving an identical equilibrium constant $K(\mathrm{VX}) = k_1/k_{-1} = ([\mathbf{1c}][\mathbf{1d}])/([\mathrm{VX}][\mathbf{1a}])$ of 0.86−0.88 (Table S-7, Supporting Information). However, the calculated K values from the other samples in Table S-7 are not constant, because *K* values are dependent on the solvent system, which determines the activity coefficients of the four components.[11] Samples 1 and 2 were of similar compositions, and the *K* values were the same. The *K* values differ significantly for the other samples, particularly in samples 5 and 6 with added water, which hydrogen bonds to both **a** and **d** and might have deactivated these nucleophiles.[11,12]

(3) Hydrolysis and Nucleophilic Substitution of 1c. Base- and Acid-Catalyzed Hydrolysis in Water. The above results indicated that, contrary to the V-agent, the hydrolysis rate of **1c** (eq 2) increased as the water content in the mixture increased. When water was initially added to VX, the impurity **1c** (0.3−4.3 area %, Table S-1, Supporting Information) in VX hydrolyzed rapidly before any significant amounts of VX began to react. However, in pure water, **1c** hydrolyzed slowly with an initial half-life of about 6 h at 23 °C (Table 1). The observed rapid hydrolysis of **1c** in the VX−water mixtures might have been catalyzed by the amino group in VX and in **1d**. We therefore examined the hydrolysis **1c** in various mixtures (Table 1). In pH 12 solutions containing OH^-, Et_3N, and Et_2NH (pK_a 10.78 and 10.98 at 25 °C, respectively),[13] the hydrolysis rate was too fast to be measured accurately.

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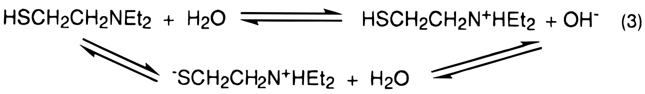
[11] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH Publishers: New York, 1988; Chapter 5.

[12] Ritchie, C. D. In *Nucleophilicity*; Harris, M. J., McManus, S. P., Eds.; Advances in Chemistry Series; American Chemical Society; Washington, D.C., 1986; Chapter 11.

[13] Riddick, J. A.; et al. *Organic Solvents: Physical Properties and Methods of Preparation, Techniques of Chemistry*, 4th ed.; Wiley-Interscience: New York, 1986; pp 638 and 625−626.

In the less basic solution of **2d** (eq 3, pK_a of $HSCH_2CH_2N^+HEt_2$ is 8.3 at 25 °C),[11] a half-life of 42 min was measured. In addition, **2d** is both a base and a nucleophile that competed with water in reacting with **1c** to produce 28% $MeP(O)(OEt)(SCH_2CH_2NEt_2)$, a V-type product. This reaction is also consistent with the reverse reaction path (k_{-1}) shown in eq 1. The rate ratio of **1c** with water (r_w) to **1c** with **2d** (r_d) is equal to the fraction of **1c** reacted with water divided by the fraction of **1c** reacted with **2d** and is calculated from the measured product ratio (Table 1).



(3)

Hydrolysis of 1c in Organic and Final Product Mixtures. In organic media such as **1a**, **2d**, and the equimolar mixtures of **1a** and **2d** containing small amounts of water (Table 1), **1c** reacted more rapidly than in aqueous solutions, probably because both water and **2d** were more reactive nucleophiles in these aprotic solvents in the absence of extensive hydrogen bonding.[11] The hydrolysis rate and the yield of **1a** also increased with the water contents in these mixtures. As shown in Table 1, about 5000 ppm **1c** was added to an authentic final product mixture and reacted rapidly with a half-life of 20 min, a rate comparable to that in the mixtures of **1a** and **2d**. Only 2% VX was produced from reaction with **1d**, indicating that hydrolysis of **1c** by the residual water present in this final product sample was so rapid that the reaction between **1c** and **1d** was almost too slow to compete.

(4) Hydrolysis of *O,S*-Diethyl Methylphosphonothioate (3, MeP(O)(OEt)(SEt)). The composition of an equimolar mixture of the thioate analog **3** and water remained unchanged at room temperature over a period of 3 months. When about 1500 ppm of pure **3** was added to a sample of the final VX−water reaction mixture (initial composition: $H_2O/VX = 0.10$ g/g, reaction time 60 days)) the spike remained unreacted at room temperature for 12 days. As shown in Table S-1 (Supporting Information), **3** was a minor impurity in VX, and about the same amount of **3** was found in the final product by both GC/MS and ^{31}P NMR. In addition, a mixture of **3**, Et_3N, H_2O, and **1a** at molar ratios of approximately 1:1:1:0.2 was prepared (a single phase mixture). The mixture was allowed to react at 40 °C for 5 days. Little conversion of **3** and no formation of **1c** could be detected by ^{31}P NMR. It can be concluded that **3** does not react with **1a** or **1b** (i.e., the anion of **1a**, see Scheme 1) under similar reaction conditions as the V-agents even when an external amine was present.

Discussion

Chart 1. Intramolecular Base-Catalyzed Hydrolysis

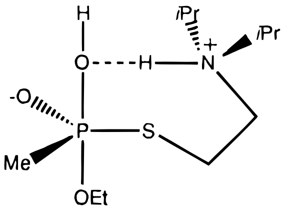
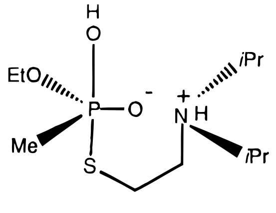
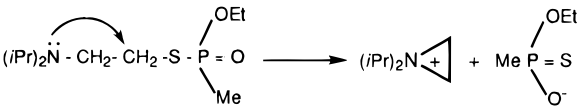


Chart 2. Intramolecular Electrostatic Interaction



It has been extensively demonstrated that, in dilute aqueous solutions at neutral to weakly basic pH, both VX and VXH^+ (Scheme 1, pK_a 8.6 at 25 °C) hydrolyze completely within 1 week with an initial observed pseudo-first-order rate constant of 3.21×10^{-6} s^{-1} at 23 °C.[9,14,15] The reaction can occur via cleavage of the P−S, P−O, and S−C bonds. In addition to the bimolecular reaction with OH^- at the phosphorus ($k_{OH} = 5.19 \times 10^{-3}$ M^{-1} s^{-1}) that gives two leaving groups at a constant P−S/P−O cleavage ratio of 88/12,[9,16] the hydrolysis is promoted by the intramolecular amino group via at least three additional independent reaction pathways: (a) neighboring nitrogen-assisted displacement to cleave the S−C bond (eq 4, $k_o = 4.6 \times 10^{-7}$ s^{-1}, a minor path except at elevated temperatures);[9,14,17] (b) general-base catalysis with the *O*-ethyl group departing from the apical position opposite to the attacking H_2O molecule (Chart 1, $k_{ib} = 3.59 \times 10^{-6}$ s^{-1});[8,9] and (c) electrostatic stablization in VXH^+ with the *S*-alkyl group departing from the apical position opposite to the attacking hydroxide ion (Chart 2, k_{ia}, appears to be of the same magnitude as k_{ib}).[18] At low $[OH^-]$ (pH 7−9) and 23 °C, the observed reaction results mainly from the two latter pathways as depicted in Charts 1 and 2 to give final products at P−S/P−O of approximately 45/55.[9] This is further supported by the fact that no reaction was detected in a dilute aqueous solution of **3**, which is neutral and does not contain an amino group, for at least 7 months at room temperature. (Note that in basic solutions, **3** reacts with the OH^- via the same mechanism as VX with $k_{OH} = 3.35 \times 10^{-3}$ M^{-1} s^{-1} at 23 °C and gives products at a constant P−S/P−O ratio of 76/24).[9,16]



(4)

In this investigation, only a small amount of water was present so that the V-agents were the dipolar and aprotic solvents in these mixtures. VX did not react with either water or OH^- directly because no product from P−O cleavage was observed (a small amount of **4** was observed

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(14) Epstein, J.; Callahan, J. J.; Bauer, V. E. *Phosphorus* **1974**, *4*, 157−163.

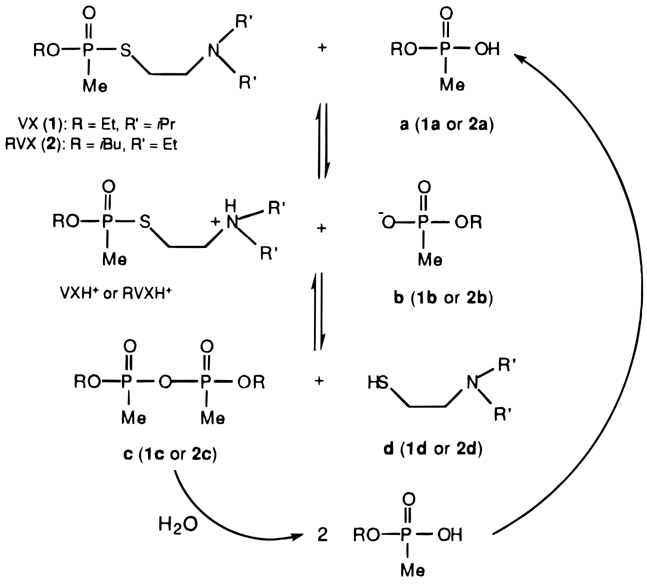
(15) Szafraniec, L. J.; Szafraniec, L. L.; Beaudry, W. T.; Ward, J. R. *On the Stoichiometry of Phosphonothiolate Ester Hydrolysis*, CRDEC-TR-212, July 1990, Aberdeen Proving Ground, MD, unclassified report.

(16) Yang, Y.-C.; Szafraniec, L. L.; Beaudry, W. T.; Bunton, C. A. *J. Org. Chem.* **1993**, *58*, 6964−6965.

(17) The reaction shown in eq 4 is truly unimolecular. Hydrolysis of 0.02 M VX in 25% $H_2{}^{18}O$ at 22 °C gives the following mixture at 54% VX conversion: **1a** (δ_P 27.581; 27.543) and **4** (δ_P 43.468; 43.430) with 25% ^{18}O incorporation in each compound; and MeP(S)(OEt)OH (δ_P 76.478) and the remaining VX (δ_P 61.933) without any ^{18}O incorporation.

(18) Lazarus, R. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 4300−4311.

Scheme 1. Autocatalytic Hydrolysis Mechanism for Mixtures of Equimolar Water and V-agent

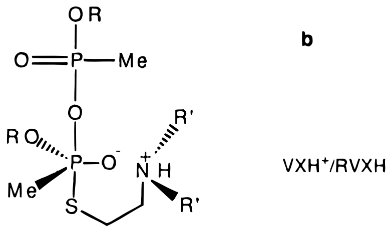


but was produced from an impurity).[19] Furthermore, the initial rate decreased when the amount of added water increased (e.g., Figure 3), but increased when **2a** was added to the RVX−water mixture (Figure 2). Therefore, the reaction is believed to be initiated by the attack of the anionic nucleophile **b** on the protonated V-agents (VXH^+ or $RVXH^+$) to produce the diphosphonate **c**, observed as an intermediate. The reactive **c** rapidly hydrolyzes to regenerate **a**, an effective nucleophile when deprotonated, and the ionic chain reaction continues (Scheme 1). The initial amount of **a** in these mixtures came from the rapid hydrolysis of **c**, an impurity in the V-agent, after water is added. Since the conjugate base of the product **a** (i.e., **b**) is the reactant in the first and rate-determining step, the reaction is autocatalytic.

The reaction rate profiles in Figure 2 also support an autocatalytic process. The observed rate was slow initially because the concentration of **a** was small, but the rate increased when the reaction proceeded with increased amount of **a**. The reaction became slow again at the final stage because the concentration of the V-agent was low and the reaction mixture became more viscous and more acidic. A more rapid rate was observed in mixtures with less water because the anionic **b** is a more reactive nucleophile in the absence of water.[11,12] The viscous final mixture and the observed reduction in final volume indicate that the major products **a** and **d** are probably present as a tight ion pair with little residual water to solvate the charges.

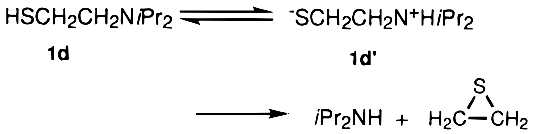
When water was insufficient and had been consumed, the V-agent was regenerated from the reaction of **c** and **d** and the degradation of the V-agent was incomplete. Therefore, the driving force for the observed V-agent−water reaction is the rapid hydrolysis of **c**. As shown in eqs 1 and 2, in the absence of water, an equilibrium is reached and $k_1/k_{-1} = K$ (Table S-7, Supporting Information); in the presence of water, $k_2 > k_{-1}$, and the reaction is irreversible (note k_2 increases in the presence of the V-agent, R'_2NH, and **d** (see Table 1)). The observed VX degradation under storage conditions must be very close to the equilibrium shown in eq 1. All four components, VX, **1a**, **1c**, and **1d**, should be present in equilibrium concentrations in the container. As trace amounts of water slowly seep into the VX, both reactions in eqs 1 and 2 will occur until the water is depleted and the equilibrium in eq 1 is reestablished.

Chart 3. Proposed Intramolecular Electrostatic Interaction in the Substitution Step

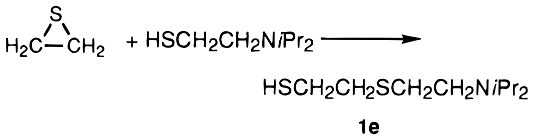


An electrostatic effect similar to that shown in Chart 2 for dilute aqueous solutions is probably more important in these organic media than in the dilute aqueous solutions of V-agents. As the protonated V-agent is attacked by **b** at the axial position of a trigonal bipyramid (Chart 3), an internal ion-pair is formed so that the positively charged amino group can stablize the negatively charged phosphoryl oxygen in the equatorial position.[18,20] This leads to the cleavage of the P-S bond in the axial position opposite to the attacking nucleophile **b**. In this rate-determining step, RVX reacted slightly faster than VX probably because the ethyl groups are less sterically hindered. Lacking an internal amino group, **3** did not react under comparable conditions even at 40 °C. Apparently, neither the *O*-ethyl group nor the *S*-alkyl group in the phosphonothioate can be displaced by **b** without the assistance of the intramolecular amino group. This is supported by the fact that the diester impurity in VX, $MeP(O)(SCH_2CH_2N\text{-}i\text{-}Pr_2)_2$, reacted rapidly.

In the final nonaqueous mixtures, the **1d** further decomposes via neighboring sulfur assistance and the formation of a zwitterion intermediate, **1d′** (eq 5), to produce the highly reactive ethylene sulfide that immediately adds onto another **1d** molecule to give **1e** (eq 6). Should the concentration of **1e** accumulate via increased degradation of **1d**, it can also react with the ethylene sulfide to eventually form polymeric thiols that may be highly viscous or even solids. Furthermore, the thiols can be air oxidized to various disulfides (e.g., **1f**−**1h**). Therefore, the composition of the final products can become more complicated as the samples age or are subjected to high temperatures, which accelerate degra-


(5)

$$\underset{\mathbf{1d}}{HSCH_2CH_2N\,iPr_2} \rightleftharpoons \underset{\mathbf{1d'}}{{}^{-}SCH_2CH_2N^+H\,iPr_2} \longrightarrow iPr_2NH + H_2C\!-\!CH_2\,(S) \quad (5)$$


(6)

$$H_2C\!-\!CH_2\,(S) + HSCH_2CH_2N\,iPr_2 \longrightarrow \underset{\mathbf{1e}}{HSCH_2CH_2SCH_2CH_2N\,iPr_2} \quad (6)$$

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[19] Although a small amount of VX could be present in the bottom aqueous phase at the initial stage of the reaction and could conceivably react with water directly (Table S-7, Supporting Information), a large amount of **1a** was also present in this aqueous phase and was expected to compete with water in reacting with the VXH^+.

[20] Thatcher, G. R.; Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99−265.

dation. Elevated reaction temperatures may be expected in large-scale systems (e.g., ton-size containers) because the heat of reaction cannot be dissipated as rapidly as in smaller reactors. External cooling or feeding the water incrementally to the VX may be considered as possible means to control the reaction temperature.

Although **d** decomposed to secondary products when the final mixture was heated, no reversible pathways to reform the V-agent existed because **a** could not react with **d** nor could it be converted to the reactive **c**. The V-agent can only be regenerated from **c**, which is absent as long as a stoichiometric amount of water is added to the V-agent to drive the reaction to completion. The autocatalytic hydrolysis of V-agents in equimolar water is irreversible at both room temperature and 90 °C.

Conclusions

Both V-type nerve agents, VX and RVX, hydrolyze completely in the presence of a stoichiometric amount of water to produce two major nontoxic compounds, **a** and **d**, that are present in the final nonaqueous solution as an ion-pair. At ambient conditions, the reaction is slow and takes about 30−60 days to reach completion, but the mechanism is autocatalytic. The first and rate-determining step is the attack of **b** on the protonated V-agent via the assistance of the intramolecular amino group. A toxic reaction intermediate **c** is produced and rapidly hydrolyzes to **a**, which is the carrier of the chain reaction. The final mixture remains reactive toward freshly added trace amounts of V-agent and **c**, both of which are absent in the final products. In case the added water is depleted before all of the V-agent has reacted, **c** accumulates and reacts with **d** to reform the V-agent until an equilibrium is established among the four major components in the dry mixture: the V-agent, **b**, **c**, and **d**. A slight excess over the required equimolar water is recommended to ensure irreversibility.

This autocatalytic hydrolysis reaction is unique and selective to only those organophosphorus esters with similar structures as the V-type agents (i.e., an intramolecular amino group is essential) and involves both intra- and intermolecular-catalyzed reaction steps. We recommend application of this chemistry in the large-scale neutralization of V-agent stockpiles *in-situ* (i.e., inside the original containers). Postprocessing of the final products by chemical, biological, or thermal methods is also recommended so that the final wastes to be disposed of may not pose any adverse effect to the natural environment.

Experimental Section

Materials. Compounds **1**−**4**, **1c**−**e**,**g**−**h**, and **2a**,**c**,**d** were prepared in-house and were 91−96 mol % pure by ^{31}P and/or ^{13}C NMR. The composition of the V-agents **1** and **2** by NMR are listed in Tables S-1 and S-2 (Supporting Information), respectively. Both V-agents are clear, nonvolatile, organic liquids with specific gravities 1.01 for VX and 1.00 for RVX. Preparation procedures for compounds used are not reported here for safety reasons. CAUTION: (a) compounds **1**−**4**, **1c**, and **2c** are toxic to exceedingly toxic; (b) some of the less toxic compounds or their precursors can be used to prepare the V-type agents; and (c) syntheses of some of the other compounds require preparation of intermediates that are either much more toxic or can be used as precursors for the preparation of the V-type agents. Of the commercially available compounds used, **1a**, diethylamine ($(C_2H_5)_2NH$, 99%), triethylamine ($(C_2H_5)_3N$, 99%), and diethyl methylphosphonate ($CH_3P(O)(OC_2H_5)_2$, 97%) were obtained from Aldrich Chemical Co. and used as received. $H_2{}^{18}O$ was from MSD Isotopes Co. and was 96 atom % in ^{18}O. Triply distilled water was used. Additional Experimental details are provided as Supporting Information.

Acknowledgment. The authors thank the Toxicology Team, ERDEC, for determining the toxicity of the product samples; Mrs. Ann B. Butrow for measuring the viscosities and densities of a large number of samples; Mr. Leonard J. Szafraniec for the preparation of **1c**, **2**, **2d**, **3**, and **4**; Mr. David I. Rossman for the preparation of **1e** and **1f**; Dr. Fu-Lian Hsu for the preparation of **1d** and **2d**; and Dr. Frederic J. Berg for the preparation of **2a** and **2c**.

Supporting Information Available: The rest of the Experimental Section including experimental procedures, instrumentation, a detailed investigation in the phase separation phenomenon of the VX-water system, Tables S-1−7, and Figure S-1 are available. The compositions of the V-agents and/or the final reaction products by ^{31}P NMR and GC/MS/CI analyses are listed separately in Tables S-1−3 and S-5. Representative ^{31}P and ^{13}C NMR shift values for compounds identified in the final mixtures are listed in Table S-4. Table S-6 summarizes the NMR analyses of samples taken from a 50 mL VX sample to which up to 4 mL water was added incrementally. The final equilibrium concentrations and calculated K values for samples 1−6 are summarized in Table S-7. The ^{31}P NMR spectra of the reacting RVX spike in a final RVX-water reaction mixture is presented in Figure S-1 (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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