Perhydrolysis of Nerve Agent VX

Yu-Chu Yang,* Linda L. Szafraniec, and William T. Beaudry

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

Clifford A. Bunton

Department of Chemistry, University of California, Santa Barbara, California 93106-9510

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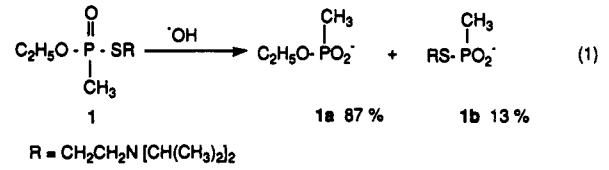
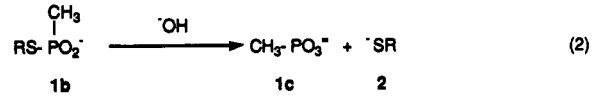
Summary: The exceedingly toxic nerve agent VX (*O*-ethyl *S*-(2-diisopropylamino)ethyl methylphosphonothioate) cannot be detoxified by reaction with hydroxide ion but is rapidly detoxified by perhydrolysis (substitution with HO_2^-) presumably via an intramolecular oxygen transfer which precludes loss of the ethoxy group.

Most chemical nerve agents (acetylcholinesterase inhibitors)[1] are P(V) organophosphorus derivatives which are effectively detoxified by hydrolysis in alkali.[2,3] One of the most toxic and least volatile nerve agents, O-ethyl *S*-(2-diisopropylamino)ethyl methylphosphonothioate (VX, 1 in eq 1), however, cannot be detoxified by reaction with



(1)

excess hydroxide ion.[4,5] With 0.01 M VX and aqueous 0.1 M NaOH, the half-life at 22 °C is 31 min (Table I), too long for battlefield decontamination.[2] In addition to displacement of the thioalkyl group (SR (R = $CH_2CH_2N[CH(CH_3)_2]_2$) in eq 1), the *O*-ethyl group also leaves, producing 13% of **1b** (*S*-(2-diisopropylamino)ethyl methylphosphonothioate ion, also toxic).[5] Although **1b** reacts with ^-OH to produce nontoxic **1c** and **2** (eq 2, **2** is



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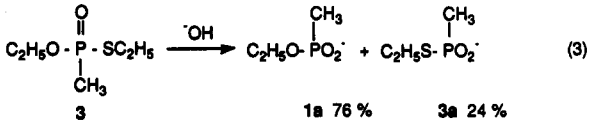


(3)

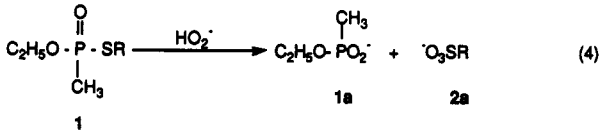
subsequently oxidized to the disulfide by air), the reaction is so slow that toxic **1b** persists for months in basic solutions (Table I). The same parallel hydrolysis paths are also observed with a less toxic VX analog, *O*,*S*-diethyl methylphosphonothioate (**3** in eq 3),[5,6] which reacts more slowly than VX (see Table I).

Table I. Hydrolysis Rate of VX and Derivatives in Basic Solution at 22 °C[a]

substrate, 0.01 M	[NaOH], M	k_{OH}, s^{-1}, M^{-1}	
VX	0.10 to 1.0	$(4.12 \pm 0.08) \times 10^{-3}$ [b]	(31 min)[c]
1b	0.25 to 1.25	$(1.1 \pm 0.2) \times 10^{-6}$	(7.4 days)[d]
3	0.10 to 1.0	$(2.67 \pm 0.05) \times 10^{-3}$ [e]	(48 min)[c]

[a] The observed rate constant, k_{obs}, was monitored by ^{31}P NMR; $k_{obs} = k_{OH}[^-OH]$. [b] A larger k_{OH} value was reported for dilute hydroxide solutions in ref 4. [c] Value in parentheses is $t_{1/2}$ in 0.1 M NaOH. [d] Value in parentheses is $t_{1/2}$ in 1.0 M NaOH. [e] Ionic strength was controlled at 1 M $NaNO_3$.

Consequently, we examined perhydrolysis (HO_2^- substitution) of VX as an alternate detoxification method because peroxy anions are effective α-nucleophiles toward P(V) esters.[7-9] At 22 °C, reaction of 0.01 M VX with 0.097 M HO_2^- (in 0.1 M NaOH and 1% H_2O_2 ($pK_a = 11.8$), [O] = 0.31 M by titration) was so rapid that 90% of the VX reacted in 2.5 min. Not only was the rate ($t_{1/2} \sim 42$ s) increased about 40-fold relative to hydrolysis at the same pH, but, more importantly, a single reaction formed nontoxic products (eq 4) with exclusive displacement of



(4)

the SR group. Therefore, we recommend perhydrolysis for VX detoxification and offer an explanation for the observed reaction.

On the basis of ^{31}P and ^{13}C NMR analyses, **1a** and **2a** (eq 4) were the major products.[10] Under the reaction conditions, the amino group was partially protonated, and a small amount of the *N*-oxide of **2a** was also produced. These major products are those from the oxidation of VX by peracids.[5] In the same study, we also reported that VX

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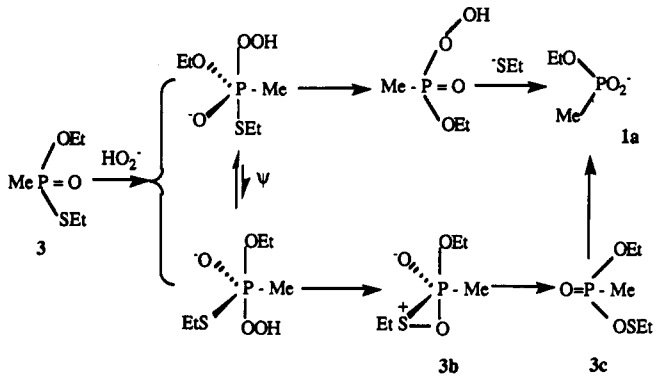
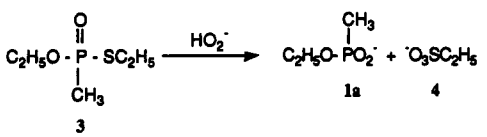
(10) In addition to **1a**, signals of three distinct diisopropylamino moieties were present in the ^{13}C spectrum of the final solution (see supplementary material, Table S-I). They were tentatively assigned as 84% **2a** (CH_3, 21.7; CH, 52.6; NCH_2, 54.7; $CH_2SO_3^-$, 44.0), 11% of the *N*-oxide of **2a** ($(CH_3)_2$, 19.4, 19.5; CH, 69.7; CH_2, 56.6), and 5% sulfenate, $^-O_2SCH_2CH_2N(CH(CH_3)_2)_2$ (CH, 47.3; CH_3, 24.3).

Scheme I. Proposed Oxygen Transfer Mechanism in the Perhydrolysis of 3



did not react with H_2O_2 at neutral pH. We believe the rapid reaction in alkaline H_2O_2 to be substitution by HO_2^- rather than oxidation by peroxide because, for a given $[H_2O_2]$, reaction is slower at lower pH. Compound **2a** is probably produced by further oxidation of the $^-$SR leaving group. There was no P–O cleavage because only **1a** was detected by ^{31}P NMR. Should **1b** be produced, it would be stable in the reaction mixture because **1b** reacts with HO_2^- (see discussion later) and H_2O_2 very slowly.[11] Furthermore, if oxidation of the thiolo sulfur were rate-determining, VX should react more slowly than the anionic **1b**.[11] Therefore, reaction of VX is substitution at the P–S bond followed by oxidation of the primary product to give the same final products as those from direct oxidation.

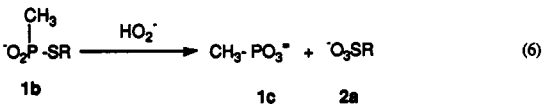
As with VX, 0.01 M **3** reacted with 0.097 M $[HO_2^-]$ rapidly via exclusive P–S cleavage (eq 5). The half-life at



(5)

22 °C was ~1.7 min, and the reactivity ratio of HO_2^- to $^-$OH was approximately 30. In the final solution, $C_2H_5S^-$ was oxidized to **4** (eq 5), which was identified by comparing its ^{13}C NMR spectrum with that of an authentic sample (see Table S-I (supplementary material) for NMR shifts). In the hydrolysis of VX or **3** (eq 1 or 3), attack by $^-$OH on the tetrahedral substrate should give a trigonal bipyramidal intermediate with apical alkoxy or thioalkyl groups that can pseudorotate.[12] Alkoxy groups ($pK_a \approx 16$)[13] are more electronegative than thioalkyl groups and prefer to be apical,[12] but the latter are better leaving groups ($pK_a \approx 12$),[4] so the net effect is preferential, but not complete, P–S cleavage. In perhydrolysis, as shown in Scheme I for **3**, initial attack by HO_2^- should also give a trigonal bipyramidal intermediate with apical alkoxy or thioalkyl groups. Conceivably, an unusual effect of the –OOH group may shift the pseudorotation equilibrium (ψ) to favor an apical thioalkyl group and force its expulsion exclusively. A peroxyphosphonate would form and be rapidly reduced, e.g., by EtS^-. On the other hand, we are inclined to postulate an alternative reaction path that will not give P–O cleavage even with an apical alkoxy group: Intramolecular oxygen transfer to sulfur, via a three-membered ring to form transient **3b** rapidly generates a very labile, mixed anhydride **3c**. This reaction path, similar to the Baeyer–Villiger reaction of ketones with hydroperoxides,[14] gives the same final product, **1a**, as direct displacement of a thioalkyl group. The proposed three-membered ring structure was previously identified in oxidations of thioate pesticide derivatives in nonaqueous solution.[15,16] In Scheme I, initial attack of HO_2^- is followed by intramolecular oxidation at sulfur, giving **3b**, or by loss of EtS^-, which is rapidly oxidized intermolecularly by the peroxyphosphonate or H_2O_2.

Coexistence of H_2O_2 with HO_2^- gives peroxide decomposition,[17] which was unimportant in rapid reactions of VX or **3** but was observed for 0.01 M **1b** (eq 6, a small



(6)

amount of the *N*-oxide of **2a** was also produced) in a mixture of 0.2 M NaOH and 0.3 M H_2O_2 (0.18 M initial HO_2^-). About 30% **1b** remained after 2 days when almost all the peroxide had decomposed.[18] On the basis of the initial rate, we estimated a half-life of 6.5 h at 22 °C. The reactivity ratio of HO_2^- to $^-$OH is about 150, much larger than those for VX and **3**. This enhanced rate ratio may be attributed to the greater dispersion of negative charge on the attacking HO_2^- relative to $^-$OH. Despite this large rate increase, perhydrolysis is not effective in detoxifying **1b**, but oxidation by peracids rapidly detoxifies **1b**.[11]

Acknowledgment. The authors thank Mr. Leonard J. Szafraniec of ERDEC for the preparation of both compounds **1b** and **3**. Partial funding from the Army Research Office and the Office of the Program Manager for Chemical Demilitarization is also appreciated.

Supplementary Material Available: ^{31}P and ^{13}C NMR spectral data for **1**, **1a**, **1b**, **1c**, **3**, and **3a**, ^{13}C NMR data for **2**, $((i\text{-}Pr)_2NC_2H_4)_2S_2$, **2a**, $^-O_3SC_2H_4N^+(O^-)(i\text{-}Pr)_2$, $^-$SEt, EtSSEt, and **4**, ^{31}P NMR data for $Me(SC_2H_4N^+(O^-)(i\text{-}Pr)_2)PO_2^-$, and a general experimental procedure (2 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.

(11) Unpublished oxidation results: (a) In 3% H_2O_2, neither VX nor **1b** reacted significantly during 8 h at 22 °C; only small amounts of the *N*-oxides of VX and **1b** were observed. (b) At 22 °C, 0.01 M VX was oxidized by 0.1 M magnesium monoperoxyphthalate ([O] = 0.17 M) in water with a half-life of 6.9 min. Under the same conditions, oxidation of **1b** was too fast to measure. Reaction products were the same as those from perhydrolysis of VX or **1b**, respectively. **1b** is also rapidly oxidized in aqueous bleach.

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(18) Peroxide decomposition is much slower in perborate than in H_2O_2, so perhydrolysis of 0.01 M **1b** goes to completion in 0.2 M sodium perborate ($NaBO_3 \cdot 4H_2O$, [O] = 0.16 M) and 0.3 M NaOH, but the half-life is approximately 12 h at 22 °C.