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Computational studies on the solvolysis of the chemical warfare agent VX

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The reaction of the chemical warfare agent VX with hydroxide and hydroperoxide has been studied using a combination of correlated molecular orbital and density functional theory. It is found that the alkaline hydrolysis leads to a mixture of neurotoxic and non-toxic products while hydroperoxidolysis leads to exclusive formation of non-toxic products. Natural bond orbital (NBO) analysis is used to rationalize the observation that hydroxide will attack opposite the alkoxide ligand, while hydroperoxide will attack opposite the thiolate. The current results are in good agreement with previous experimental and computational work and serve to clarify the mechanism for destruction of this highly potent nerve agent. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: alkaline hydrolysis; hydroperoxidolysis; nerve agent VX; pseudorotation; nucleophile; α-nucleophile

INTRODUCTION

Chemical warfare agents, particularly organophosphorus nerve agents, have come under recent scrutiny as fear of terrorist attacks has increased. VX (*O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothiolate) is a particularly lethal example. The pronounced neurotoxicity of VX stems from its chemical structure (Scheme 1), which is similar to the neurotransmitter acetylcholine (ACh). When introduced to the body, VX irreversibly binds to the enzyme acetylcholinesterase, resulting in a loss of muscle control and death by asphyxiation.[1] VX can enter the system not only by inhalation but also through direct contact with the skin. As a non-volatile liquid, VX can remain persistent in the environment for prolonged periods, in contrast to the volatile G-series agents such as sarin and tabun. Thus, efficient methods for detoxification of contaminated areas are essential. Furthermore, in accordance with the Chemical Weapons Convention of 1997, all stockpiles of VX must be destroyed, which requires a safe and effective means of detoxification.[2]

In order for VX to be rendered non-toxic, the phosphorous-sulfur (P—SR, where R is 2-(diisopropylamino)ethyl) bond must be cleaved. Alkaline hydrolysis of VX at room temperature (Scheme 2) yields a mixture in which 87% of the product is formed from P—SR cleavage (ethyl methylphosphonic acid, EMPA) and 13% from phosphorous-ethoxide (P—OEt) cleavage (*S*-(2-diisopropylamino) ethyl methylphosphonothioic acid, EA2192).[3] Unfortunately, EA2192 retains structural similarities to acetylcholine and is still a potent neurotoxin.[4] Nevertheless, the current detoxification process carried out by the U.S. military utilizes alkaline hydrolysis of VX at 90°C, followed by oxidation.[2] This elevated temperature ensures hydrolysis of both VX and EA2192. Oxidation of the resulting hydrosylate solution results in a completely non-toxic product.

Other detoxification methods have been explored using oxidizing agents,[4,5] photocatalysis,[6,7] metal-catalyzed decomposition,[8,9] enzymatic degradation,[10–12] and reduction.[13,14] In addition to technologies for destroying VX, much recent work in the field has focused on the detection of VX and its solvolysis products.[15–20] While several previous computational studies on chemical warfare agents and simulants have appeared,[8,21–26] none have examined in detail the nucleophilic chemistry of VX itself. Of particular interest is the potential kinetic competition between nucleophilic attack opposite the more electronegative alkoxide ligand and the bulkier thiolate ligand.

When a nucelophile attacks the phosphorous of a phosphonothiolate, a trigonal bipyramidal (TBP) structure may result. Barring any other effects,[27] the most electronegative ligands are expected to occupy the apical positions.[28] Thus, nucleophilic attack opposite the most electronegative ligand is expected, placing both the nucleophile and that ligand in the apical positions. In the case of VX, it is expected that nucleophilic attack should occur opposite the ethoxide group.[29] Ligand elimination is also favored from an apical position, therefore, this initial attack would appear to favor P—OEt cleavage. However, it is evident from experimental data that P—SR cleavage is actually dominant, regardless of whether the nucleophile is hydroxide or hydroperoxide.[3,30,31] It is hypothesized that after the initial nucleophilic attack and TBP formation, a pseudorotation[32] occurs that places the ethoxide in an equatorial position and moves the thiolate group into an apical position for facile cleavage. If this process is energetically more favorable than P—OEt cleavage, the product distribution will shift to give a majority of P—SR cleavage. Indeed, this is the case with the VX simulant

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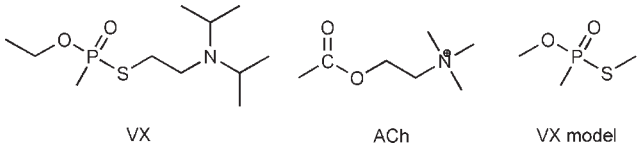
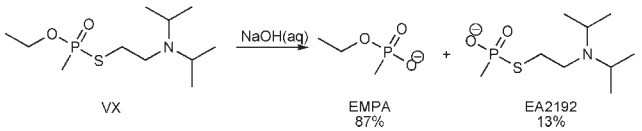


Scheme 1. Structures of VX, acetylcholine, and VX model *O,S*-dimethyl methylphosphonothiolate



Scheme 2. Alkaline hydrolysis of VX

O,S-dimethyl methylphosphonothiolate.[24] It is possible that other steric or electronic factors may negate the expected apicophilic preference. For example, in VX, the bulky (diisopropylamino)ethyl chain may sterically hinder the attack of a nucleophile when the bulky ligand is in a pro-equatorial position. If, instead, the nucleophile attacks opposite the thiolate group, then the large amino chain is as far removed from the nucleophile as possible. Thus, there may be a preference in VX for nucelophilic attack opposite the bulkiest ligand. With the thiolate chain now in an apical position, cleavage of the P—S bond would be the dominant process.

Alpha-nucleophiles, those containing an atom with lone pairs adjacent to the nucleophilic atom, have proven effective in the destruction of VX and VX simulants.[30,33] For example, when reacted with a solution of hydroperoxide at room temperature, exclusive P—SR cleavage is observed, resulting in a fully non-toxic product.[3,30,31,34] Computational studies on a model system of VX have helped rationalize the differences in product distribution during reaction with a prototypical normal nucleophile (hydroxide) and a simple α-nucleophile (hydroperoxide).[24] It was found that both nucleophiles attack the phosphorous preferentially forming a TBP intermediate with the nucleophile and alkoxide apical, in accordance with apicophilic expectations. The alkoxide ligand can then be cleaved or a pseudorotation can take place shifting the thiolate chain into the apical position, resulting in P—SMe cleavage. In the case of hydroxide attack, the pseudorotation and resulting P—SMe cleavage is only slightly favored relative to the direct P—OMe cleavage process, resulting in products from each. However, during hydroperoxidolysis, P—OMe cleavage no longer competes with pseudorotation and P—SMe cleavage, resulting in exclusive loss of the thiolate ligand. Furthermore, a second, even more favorable pathway was discovered that would lead to P—SMe cleavage via a somewhat unusual intramolecular rearrangement.

We now report on the alkaline hydrolysis and hydroperoxidolysis of the full VX molecule. Our chief goal is to clarify the steric or electrostatic role that the pendant (diisopropylamino)ethyl chain may play.[23] Our results do illustrate that a favorable interaction between the amino group and the nucleophile is possible, leading to a certain degree of self-catalysis. It is further discovered that the two nucleophiles no longer display the same preference for initial attack, possibly due to the increased steric bulk of the thiolate chain. Important comparisons are drawn between this work and prior work on model systems.

COMPUTATIONAL METHODS

All geometries were optimized using the MPW1K[35] density functional and the MIDI![36] basis set. Harmonic frequency calculations at this same level were used to confirm the stationary points and provide thermodynamic corrections. Intrinsic reaction coordinate (IRC) calculations[37] were performed to ensure the connections between transition states and minima. More accurate electronic energies were obtained via single-point calculations at the MP2/6-31+G(d) level of theory.[38,39] Aqueous free energies of solvation of the gas-phase structures were determined at the HF/6-31+G(d) level of theory with the integral equation formalism polarizable continuum model (IEF-PCM) using the UFF topological model,[40] which creates an explicit sphere on each atom. This combination of theories has been shown to work well for modeling similar chemistry.[24] All energies discussed are solvated enthalpies corrected to 298 K in order to facilitate comparison with previous work. For selected transition states, natural bond orbital (NBO) analyses of second-order interaction energies and steric repulsion energies were obtained. All calculations were performed using Gaussian 03,[41] except for the NBO analysis which was performed using the stand-alone GENNBO program,[42] both under the Mac OSX operating system.

RESULTS AND DISCUSSION

The optimized structures for the most important stationary points on the alkaline hydrolysis and hydroperoxidolysis pathways are presented in Figures 1 and 2, respectively. Reaction coordinate diagrams are shown in Figures 3 (alkaline hydrolysis) and 4 (hydroperoxydolysis). The reaction coordinate diagrams also include relative enthalpies at 298 K, corrected for aqueous solvation. Further geometric and energetic details are available as supporting information. Selected NBO analyses are presented in Tables 1 and 2. The rest of this section will focus on the individual results for the reactions of hydroxide and hydroperoxide with the nerve agent VX and a short comparison to the results obtained in the previous study[24] using the VX model, *O,S*-dimethyl methylphosphonothiolate.

Alkaline hydrolysis

Several modes of hydroxide attacking VX opposite the thiolate and ethoxide ligands were initially considered, differing only in the position of the pendant thiolate side chain. Three stationary point transition states were located: one for attack opposite the thiolate ligand (**TS1a**) and two for attack opposite the ethoxide ligand (**TS1b** and **TS1c**). The diisopropylamino moiety is positioned to stabilize the attacking hydroxide in **TS1b**, while it is rotated well out of the way in **TS1c**. Due to this stabilization, **TS1b** lies more than 7 kcal/mol lower in energy than **TS1c**. Therefore, the remainder of the discussion will focus on the competition between the pathways involving **TS1a** and **TS1b**, and will ignore the energetically disfavored **TS1c**.

The transition state for attack opposite the thiolate ligand (**TS1a)** has a relative enthalpy of 21.0 kcal/mol above the separated reactants, and a P—OH bond length of 2.698 Å, slightly longer than the P—S bond of 2.171 Å. This transition state collapses to form a TBP intermediate (**2a**) with the thiolate chain in the apical position and a relative enthalpy of −4.4 kcal/mol. In

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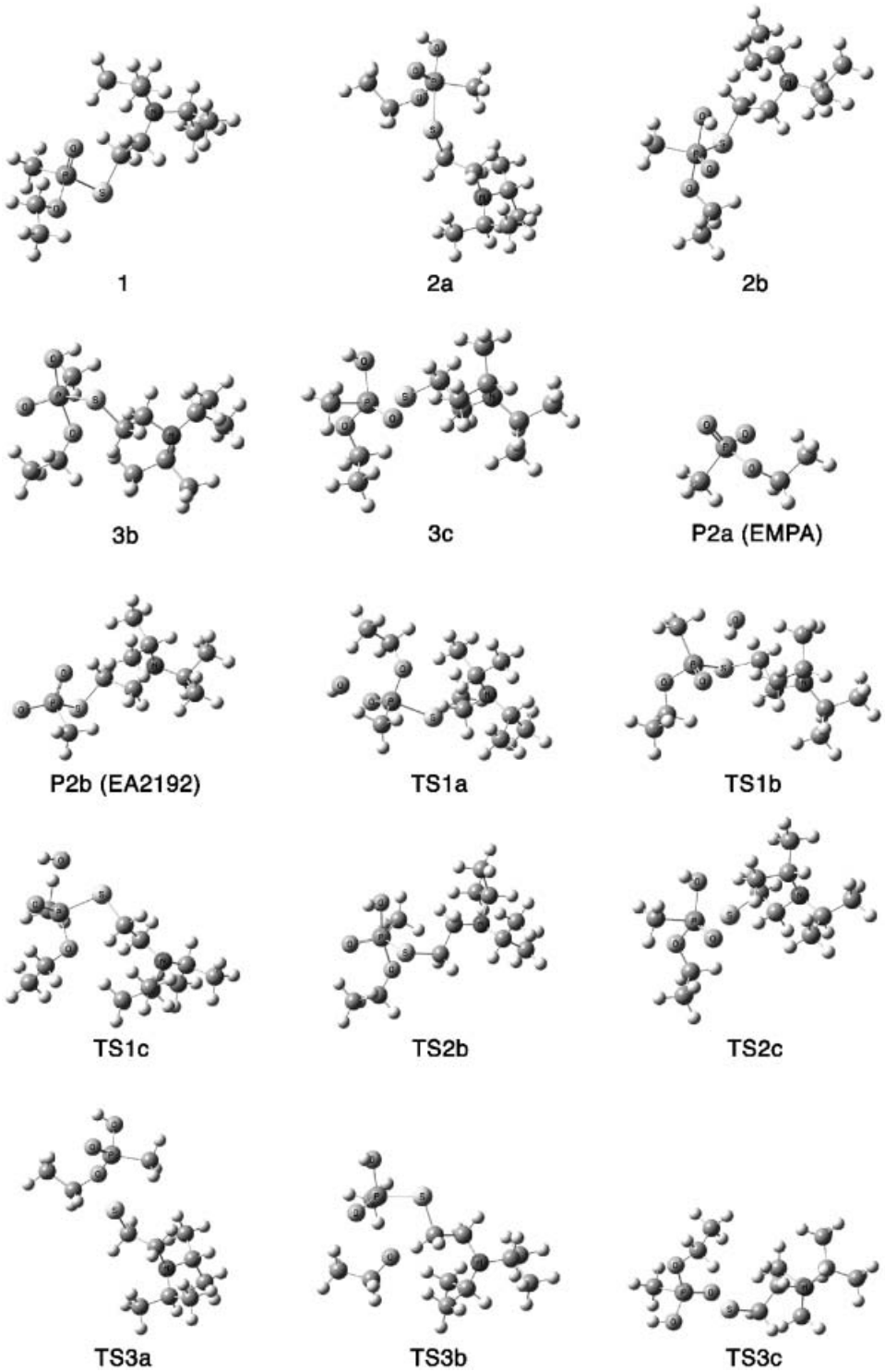

Figure 1. Stationary points for the alkaline hydrolysis of VX

2a, the P—OH bond has shortened to 1.726 Å, which is nearly 1 Å shorter than in the attack transition state, while the P—S bond has lengthened slightly to 2.425 Å. It was found that loss of the thiolate ligand from **2a** proceeds in a barrierless fashion. In fact, the transition state for P—SR bond cleavage (**TS3a**) has a relative enthalpy of −11.3 kcal/mol, placing it well below **2a**. IRC calculations confirm that **2a** does connect to **TS3a**. Thus, the seeming discrepancy that **TS3a** lies below **2a** is most likely due to the fact that gas-phase geometries have been used and the true solvated stationary point would be found at a different point on the reaction coordinate. The same situation was observed in the alkaline hydrolysis of the model system.[24]

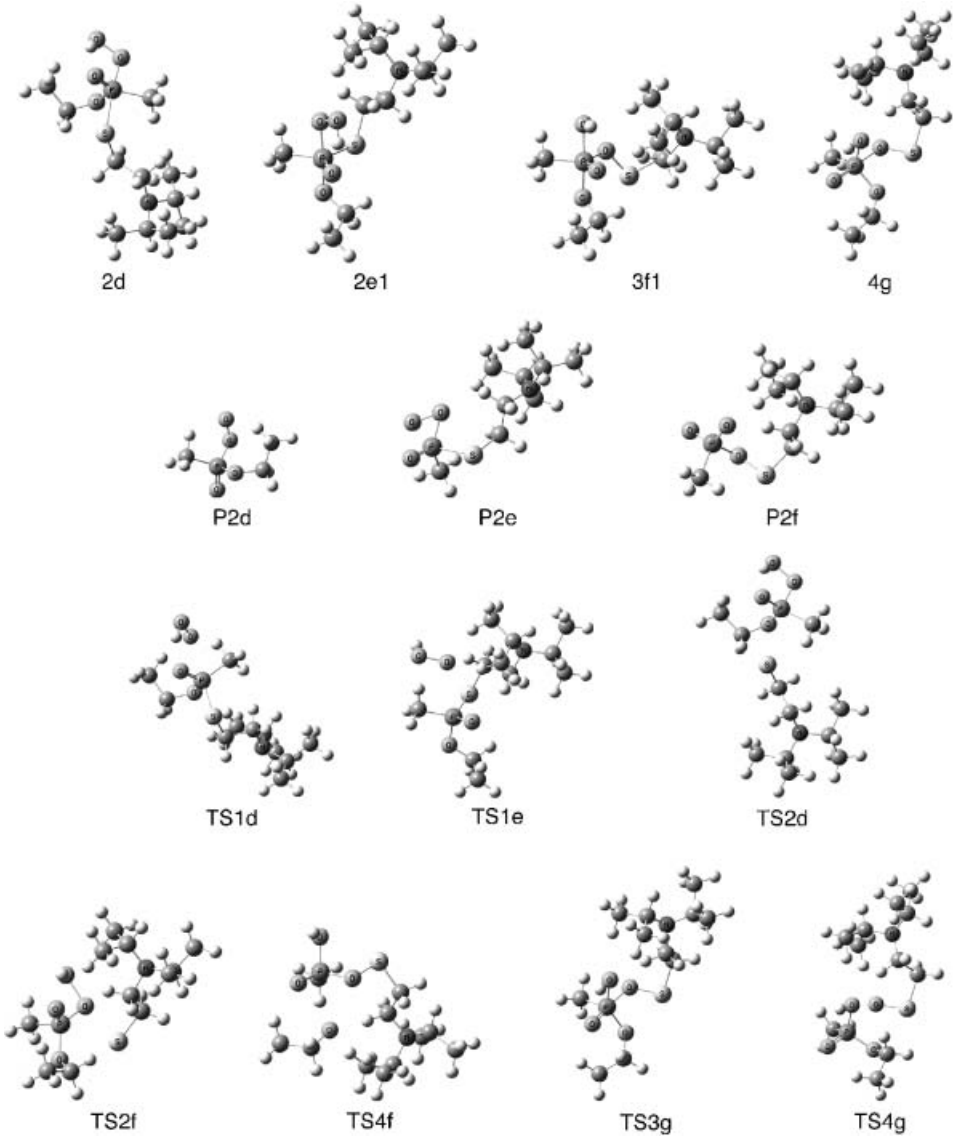

Figure 2. Stationary points for the hydroperoxidolysis of VX

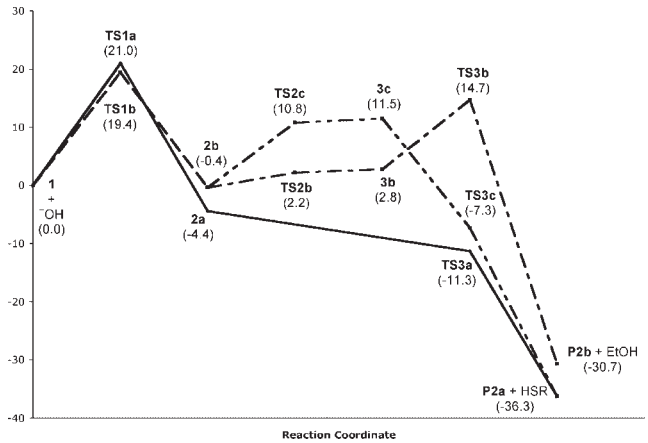

Figure 3. Reaction energy diagram for the alkaline hydrolysis of VX

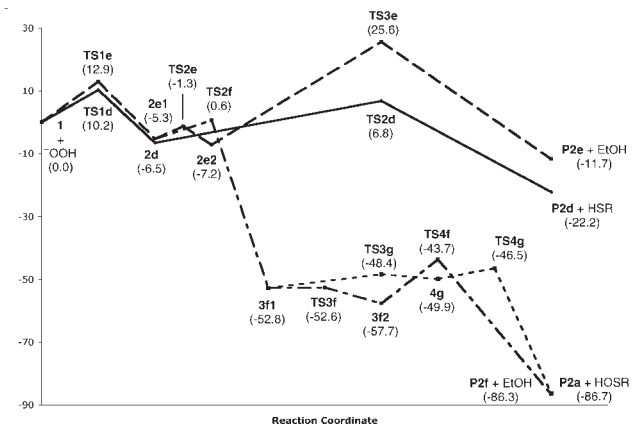

Figure 4. Reaction energy diagram for the hydroperoxidolysis of VX

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Regardless, **TS3a** has a P—OH bond distance of 1.688 Å and a P—S bond distance of 2.955 Å, indicating an early transition state (i.e., similar in structure to **2a**) as would be expected for an exothermic reaction in accordance with the Hammond Postulate.[43] We report as the final products of P—SR bond cleavage the conjugate base of ethyl methyl phosphonic acid (EMPA, **P2a**) and 2-(diisopropylamino) ethanethiol. These isolated products lie 36.3 kcal/mol below isolated reactants.

Attack of hydroxide opposite the ethoxide ligand proceeds through stabilized transition state **TS1b** (see above), with a relative enthalpy of 19.4 kcal/mol as compared to isolated reactants. This is a slightly earlier transition state than is seen for attack opposite the thiolate ligand, with a P—OH bond distance of 2.910 Å and a P—OEt bond distance of 1.676 Å. This transition state proceeds to form TBP intermediate **2b**, lying 0.4 kcal/mol below reactants, in which the diisopropylamino group is still positioned to interact with the hydroxyl ligand. In **2b**, the P—OH and P—OEt bond distances are quite similar, at 1.778 Å and 1.781 Å, respectively. Two possibilities were now considered for the fate of **2b**: immediate cleavage of the P—OEt bond, or pseudorotation followed by cleavage of the newly apical P—S bond.

Prior to P—OEt bond cleavage, the thiolate chain rotates through **TS2b** to form a new TBP intermediate (**3b**). This new intermediate differs from **2b** only in that the diisopropylamino moiety is now positioned to stabilize the ethoxide leaving group. This portion of the potential energy surface is quite flat, with **TS2b** having a relative enthalpy of 2.2 kcal/mol and **3b** being essentially isoenergetic with **TS2b** (2.8 kcal/mol relative enthalpy). The barrier for P—OEt cleavage is found to be significant, with the transition state for this process (**TS3b**) lying 14.7 kcal/mol above isolated reactants, and also demonstrates a significantly elongated P—OEt bond (3.102 Å). The final isolated products, the conjugate base of EA2192 (**P2b**) and ethanol, are located at a relative enthalpy of −30.7 kcal/mol. It is important to note that EA2192 retains neurotoxic properties.[4]

Intermediate **2b** can also undergo any number of pseudorotations to place the thiolate ligand in an apical position. Preliminary studies led us to consider one pseudorotational pathway as most likely. In this pathway, **2b** pseudorotates through **TS2c**, of roughly square-pyramidal geometry, to form TBP **3c**, in which the methyl and thiolate ligands occupy the apical positions. This pseudorotational process is more favorable than the P—OEt cleavage pathway discussed above, in that the relative enthalpies of **TS2c** and **3c** (10.8 and 11.5 kcal/mol, respectively) are both lower than the relative enthalpy of **TS3b** (12.5 kcal/mol). As was the case for direct P—SR cleavage, loss of the thiolate ligand from **3c** is barrierless, leading to the previously discussed P—SR cleavage products.

Considered collectively, these data demonstrate significant competition among the three possible pathways. For both P—OEt and P—SR cleavage, the initial attack step is the rate-determining step, and the overall mechanism is irreversible at 298 K, due to the magnitude of the reverse activation enthalpies. Following a Curtin–Hammett analysis, the 1.6 kcal/mol difference in activation enthalpies between **TS1a** and **TS1b** indicates a 15:1 preference for initial hydroxide attack opposite the ethoxide ligand. However, given that the error inherent in the level of theory applied is approximately ±1 kcal/mol,[24] it is more prudent to conclude that there is a small, perhaps negligible, preference for attack opposite ethoxide. Any initial attack opposite the thiolate ligand will proceed immediately to P—SR cleavage products. Following formation of **2b**, the pseudoration/P—SR cleavage pathway is favored over direct P—OEt cleavage by 3.2 kcal/mol, corresponding to a 223:1 preference. Again, this difference could be smaller due to errors inherent in the theory. Assuming opposite errors of 1 kcal/mol, the gap could shrink to 1.2 kcal/mol, which still favors P—SR cleavage by a ratio of 8:1, in excellent accord with the experimental result.[3] The conclusion from the alkaline hydrolysis portion of this study is that P—OEt and P—SR cleavage compete throughout the mechanism, with a slight preference for P—SR cleavage due to the difficulty in cleaving the P—OEt bond.

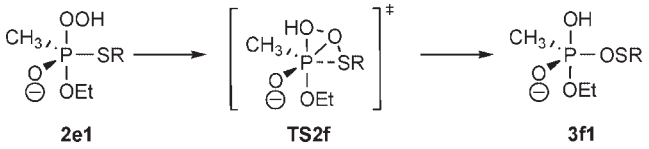
Hydroperoxidolysis

Hydroperoxide attack opposite the thiolate ligand leads to transition state **TS1d**, with a relative enthalpy of 10.2 kcal/mol. The P—OOH and P—S bond distances of 2.694 Å and 2.164 Å, respectively, are very similar to the corresponding hydrolysis structure (**TS1a**). Transition state **TS1d** leads to TBP intermediate **2d**, found 6.5 kcal/mol below isolated reactants, which has a slightly longer P—OOH bond (1.751 Å) but a significantly shorter P—S bond (2.164 Å) than the analogous **2a**. From intermediate **2d**, the P—S bond lengthens to 3.227 Å and the relative enthalpy rises to 6.8 kcal/mol as **TS2d** is formed. Final isolated products for P—SR cleavage are found 22.2 kcal/mol below isolated reactants.

Attack of the hydroperoxide ligand opposite the ethoxide ligand forms **TS1e**, which is analogous to the intramolecularly stabilized **TS1b** discussed in the alkaline hydrolysis section above. In **TS1e**, the P—OOH bond distance is 3.061 Å while the P—OEt bond distance is 1.677 Å, both of which are quite comparable to the corresponding bonds in **TS1b**. However, in contrast to alkaline hydrolysis, the relative enthalpy of **TS1e** (12.9 kcal/mol) places it above **TS1d**, indicating that hydroperoxide does not prefer to attack opposite the most electronegative ligand. The reason for this is not immediately clear. One possibility is that there are more steric contacts between the larger hydroperoxide nucleophile and the thiolate chain than are seen with the smaller hydroxide nucleophile. Increased steric repulsion could be sufficient to destabilize **TS1e** relative to **TS1d**, switching the preference for initial attack. Intermediate **2e1**, lying 5.3 kcal/mol below reactants, follows from **TS1e**.

Direct P—OEt cleavage is possible from **2e1** following a conformational reorganization to TBP **2e2** (see supporting information) through **TS2e**, with relative enthalpies of −7.2 and −1.3 kcal/mol, respectively. This process arranges the diisopropylamino group such that it can stabilize the leaving group, just as was seen for alkaline hydrolysis. The P—OEt cleavage itself has a formidable barrier, with the transition state (**TS3e**) found 25.6 kcal/mol above isolated reactants. This is the single highest point on the hydroperoxidolysis reaction energy diagram, and is 12.7 kcal/mol higher than the next highest point. Even though the overall direct P—OEt cleavage process is exothermic by 11.7 kcal/mol, it is highly unlikely that any reactants will breach the barrier presented by **TS3e**, and this portion of the potential energy surface should be considered to be completely reversible.

In prior work on the simpler *O,S*-dimethyl methylphosphonothiolate,[24] the TBP intermediate analogous to **2e1** was found to undergo an internal oxygen insertion preferentially to pseudorotation. Therefore, we considered only the insertion pathway here and did not attempt to locate competitive pseudorotational pathways. Initiated from TBP **2e1**, the nucleophilic oxygen of the



2e1 TS2f 3f1

Scheme 3. Intramolecular rearrangment pathway

hydroperoxide ligand inserts itself between the P and S atoms through a three-membered-ring transition state **TS2f**, which has a relative enthalpy of 0.6 kcal/mol (Scheme 3). Simultaneously, the alpha hydroxide group migrates to the phosphorus, ultimately resulting in the formation of the remarkably stable TBP **3f1**, which lies 52.8 kcal/mol below reactants. Phosphinyloxysulfenates such as **3f1** are not unprecedented.[44] In **TS2f**, the P—S bond is 2.818 Å, the nascent S—O bond is 2.304 Å, the forming P—OH bond is 2.487 Å, and the breaking O—O bond is 1.709 Å, indicating a substantial reorganization of electron density among the four atoms involved.

Phosphinyloxysulfenate **3f1** may now cleave the P—OEt bond to form products **P2f** and ethanol, located 86.3 kcal/mol below reactants. As in the other P—OEt cleavage pathways discussed, the pendant diisopropylamino group must first undergo a conformational change to stabilize the leaving group, in this case passing through **TS3f** to form TBP **3f2**, with relative enthalpies of −52.6 and −57.7 kcal/mol respectively. The transition state for P—OEt bond cleavage (**TS4f**) lies at a relative enthalpy of −43.7 kcal/mol before forming products **P2f** and ethanol at −86.3 kcal/mol. It is not clear whether product **P2f** would retain neurotoxicity, although it would appear to be intuitively unstable and may react further. However, no attempts were made to understand the additional chemistry that **P2f** may undergo.

TBP **3f1** may also pseudorotate. One pseudorotational path was located that places the oxide and oxysulfenate ligands apical (TBP **4g**). The pseudorotational transition state **TS3g** lies at −48.4 kcal/mol relative enthalpy, while TBP **4g** is found at −49.9 kcal/mol. There is a modest barrier for P—OSR cleavage, with the transition state for that process (**TS4g**) having a relative enthalpy of −46.5 kcal/mol relative to reactants. The isolated products of P—OSR cleavage are located 86.7 kcal/mol below isolated reactants.

The hydroperoxidolysis potential energy surface is significantly more complicated than the potential energy surface for alkaline hydrolysis. However, several conclusions are easily reached. The difference in enthalpy between **TS1e** and **TS1d** of 2.7 kcal/mol is enough to favor attack opposite the thiolate ligand by a ratio of 96:1. As discussed above, this differential could be overstated, and we again see that there is no strong preference for the nucleophile attacking opposite either the ethoxide or thiolate ligands. Any attack opposite the thiolate will lead to direct P—SR bond cleavage. Any attack opposite the ethoxide ligand will lead to internal rearrangement to phosphinyloxysulfenate **3f1**, with absolutely no competition from direct P—OEt cleavage. The difference in relative enthalpies between **TS3e** (cleavage) and **TS2f** (rearrangement) of 25 kcal/mol corresponds to a preference for rearrangement of about 10^{18}. The exact fate of **3f1** is less clear, as the difference in activation enthalpies between **TS4g** and **TS4f** is 2.8 kcal/mol, giving a 100:1 advantage for P—OEt cleavage, which may be reduced in accordance with the estimated computational error limits.

COMPARISONS

Alkaline hydrolysis versus hydroperoxidolysis of VX

There are more differences than similarities when comparing the alkaline hydrolysis and hydroperoxidolysis of VX as presented in this work. In fact, the only true similarity is that the initial attack transition states are competitive in each case. However, in the case of alkaline hydrolysis, attack opposite the more apicophilic ethoxide ligand is preferred while attack opposite the larger thiolate ligand is favored in hydroperoxidolysis. To gain an understanding of this preference switch, the NBO second-order interaction energies and steric repulsion energies between the nucleophile and VX were determined for **TS1a**, **TS1b**, **TS1d**, and **TS1e** (Table 1). The second-order interaction energy (E(2)), provides an indication of favorable Lewis acid/Lewis base interactions between molecular fragments, while the steric analysis reports unfavorable interactions between filled orbitals.[42] A similar electrostatic and steric analysis has been reported on substituted methyl phosphonofluoridates.[45]

Given that a positive E(2) energy indicates a favorable interaction, while a positive steric energy indicates a repulsive interaction, the term [E(2)—Steric] will be positive for net favorable interaction between the attacking nucleophile and VX. The difference in this term for each pair of transition states is computed such that a positive number in the final row of Table 1 indicates a stereoelectronic preference for attack of the nucleophile opposite the thiolate ligand. For hydroxide attack (**TS1a** and **TS1b**), there is a relatively small preference in favor of **TS1a**, and this is not enough to offset the unperturbed preference for attack opposite the alkoxide (see below). However, for the case of hydroperoxide attack (**TS1d** and **TS1e**), the E(2) component for attack opposite the thiolate ligand overwhelms the steric repulsion, and leads to an obvious preference for attack opposite the thiolate ligand. Therefore, the primary factor making **TS1d** more stable than **TS1e** is electronic in nature, rather than steric. Such a kinetic preference for nucleophilic attack opposite a less-apicophilic ligand in a phosphonothiolate has been proposed.[46]

The reaction energy diagram for alkaline hydrolysis illustrates a mechanism that is essentially irreversible, but with closely competing pathways. Under these conditions, the product distribution should be determined by relative enthalpies of activation rather than relative enthalpies of reaction. There are small differences in activation enthalpies among the competing processes, but attack opposite ethoxide followed by pseudorotation and eventual P—SR bond cleavage is favored by a small margin. Thus, we predict competition between P—OEt and P—SR bond cleavage, with P—SR cleavage being slightly dominant, in good accord with known experimental results.[3]

Table 1. NBO E(2) and steric energies between the nucleophile and VX (kcal/mol)

	TS1a	TS1b	TS1d	TS1e
Sum of E(2) energies	159.5	144.9	184.0	116.9
Sum of steric energies	85.2	76.7	92.9	61.2
E(2)–steric	74.3	68.2	91.1	55.7
difference	6.1		35.4	

The case of hydroperoxidolysis of VX is somewhat easier to interpret, despite presenting a more complicated potential energy surface. First, the initial attack barriers are lower than for alkaline hydrolysis, in agreement with the experimental observation that hydroperoxidolysis of phosphonothiolates is significantly faster than alkaline hydrolysis.[30,34,47] Also, not all of the computed pathways are irreversible. Direct P—OEt cleavage is found to be fully reversible, with an enthalpic barrier that is unlikely to be crossed at 298 K and certainly cannot compete with the other proposed pathways. Direct P—SR cleavage is possible, and even preferred by a slight margin in the initial attack. Two other favorable processes also lead to P—SR bond cleavage, albeit one of these cleaves the P—S bond through an insertion reaction and does not lead to loss of the thiolate ligand. Thus, all favorable hydroperoxidolysis processes lead to destruction of the P—S bond with no formation of toxic EA2192, in agreement with experimental observations.[31]

VX versus model system

In comparing this work to previous work at the same level of theory on *O,S*-dimethyl methylphosphonothiolate,[24] a few important differences are noted. First, the transition states for hydroxide attacking the model differ by 3.8 kcal/mol, with attack opposite methoxide being favored. This is a slightly larger preference for hydroxide attack opposite the alkoxide ligand than is seen in the current study. Second, hydroperoxide also displays a preference to attack opposite methoxide in the model system by the same 3.8 kcal/mol. In VX itself, the attack of hydroperoxide opposite the thiolate ligand is actually preferred.

To clarify the situation, the same NBO analysis as described above was carried out for the initial attack transition states reported for the model system. The results (Table 2) demonstrate that there is no significant difference between nucleophiles for the model system and that attack opposite the alkoxide ligand is always favored, converse to the situation for VX. This observation may explain why the differences in enthalpic barriers for attack in the model system are both 3.8 kcal/mol favoring attack opposite alkoxide, regardless of which nucleophile is used.

A further point of contrast involves the TBP intermediates formed immediately after nucleophilic attack. In the model system, the TBP with the nucleophile and alkoxide apical is either favored over the TBP with the nucleophile and thiolate apical or the two are within 1 kcal/mol of each other. The same is true in VX for attack of hydroperoxide. These observations are generally consistent with apicophilic expectations. However, a dramatic reversal of TBP stabilities is found for attack of hydroxide on VX, where TBP **2a**, with thiolate apical, is 4.0 kcal/mol more stable than TBP **2b**.

Table 2. NBO E(2) and steric energies between the nucleophile and O,*S*-dimethyl methylphosphonothiolate (kcal/mol)

	TS1c[a]	TS1d[a]	TS1e[a]	TS1f[a]
Sum of E(2) energies	140.8	164.3	158.2	183.4
Sum of steric energies	79.9	81.6	81.7	87.8
E(2)—steric	60.9	82.7	76.5	95.6
difference	−21.8		−19.1	

[a] Following the naming scheme as used in Reference [24].

It has been shown that hyperconjugation may negate apicophilicty.[27] It is also possible that simple steric effects may alter the energy landscape sufficiently to overcome apicophilic factors. To estimate the contributions from various electronic and steric effects, we again employed second-order interaction and steric energy analyses via NBO, this time on the initially formed TBP intermediates of both the model and VX systems and focusing on the interactions between the former nucleophile and the remainder of the molecule. The second-order energies were found to be nearly constant across the series, suggesting that there are no significant differences in the favorable orbital interactions between the hydroxide or hydroperoxide ligand and the rest of the system. This argues that hyperconjucative effects are constant and are not a deciding factor in relative TBP stability. The same consistency is found when comparing the steric energies, except for the **2a**/**2b** pair. Here, **2a** is less sterically crowded than **2b** by 6 kcal/mol. In every other case, the difference in steric energies is 1.50 kcal/mol or less. Thus, it would appear that the loss of apicophilic control in the alkaline hydrolysis of VX is simply due to increased steric repulsion within TBP **2b** relative to TBP **2a**.

Previously, Xiong and Zhan examined the role of sterics and electrostatics in the alkaline hydrolysis of methyl phosphonofluoridates by systematically altering the equatorial alkoxide side chain.[45] The substituents included various sized alkyl groups as well as neutral amines and positively charged ammonium groups of similar size. The most relevant comparison to this work concerns the steric effect, as we did not employ positively charged ammonium groups. Xiong and Zhan found that increasing the steric bulk of the alkoxide ligand increased the barrier for attack by roughly 2 kcal/mol, which is consistent with the difference in barriers between the model system[24] and VX. It is evident that our work and the previous work reach similar conclusions concerning how the sterics of the system affect activation barriers for solvolysis of organophosphorus species.

The remaining features of the reaction energy diagram are quite similar between the model and VX. In each case, loss of thiolate is always easier than loss of alkoxide. When hydroxide is the nucleophile, these two processes are competitive, regardless of the substrate. When hydroperoxide is the nucleophile, P—SR bond cleavage is the only viable option. The large thiolate chain in VX does perturb the system somewhat, but the effect is actually quite minor. Overall, the same mechanism is illucidated by either the model or VX, and it is apparent that nucleophilic chemistry at the phosphorus atom in VX can be accurately predicted using small model systems.

CONCLUSIONS

Mechanistic studies on the alkaline hydrolysis and hydroperoxidolysis of VX have been carried out at the MP2/6-31+G*//MPW1K/MIDI! + IEF-PCM(HF/6-31G*) level of theory. The potential energy surface for hydrolysis reveals three competing pathways, two of which lead to P—SR bond cleavage and formation of a non-toxic product (EMPA) while the third leads to P—OEt bond cleavage and a product that retains neurotoxic activity (EA2192). A mixture of products is predicted, with P—SR cleavage products being more prevalent, but not exclusive. In the case of hydroperoxidolysis, no favorable pathway leading to the neurotoxic EA2192 could be found, and the only predicted

products arise from schism of the P—S bond. All of the results are in good accord with available experimental data and serve to clarify the mechanisms by which this potent neurotoxic chemical warfare agent may be destroyed.

SUPPORTING INFORMATION AVAILABLE

Cartesian coordinates for all stationary points considered in this study and tabulation of electronic energies, enthalpy corrections, and free energies of solvation.

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