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Soft detoxification of chemical warfare agent simulants and pesticides under pressure

Sergui Mansour^a, Valmir B. Silva,^{a,b} Elisa S. Orth^{b,*} and Julien Legros^{a,*}

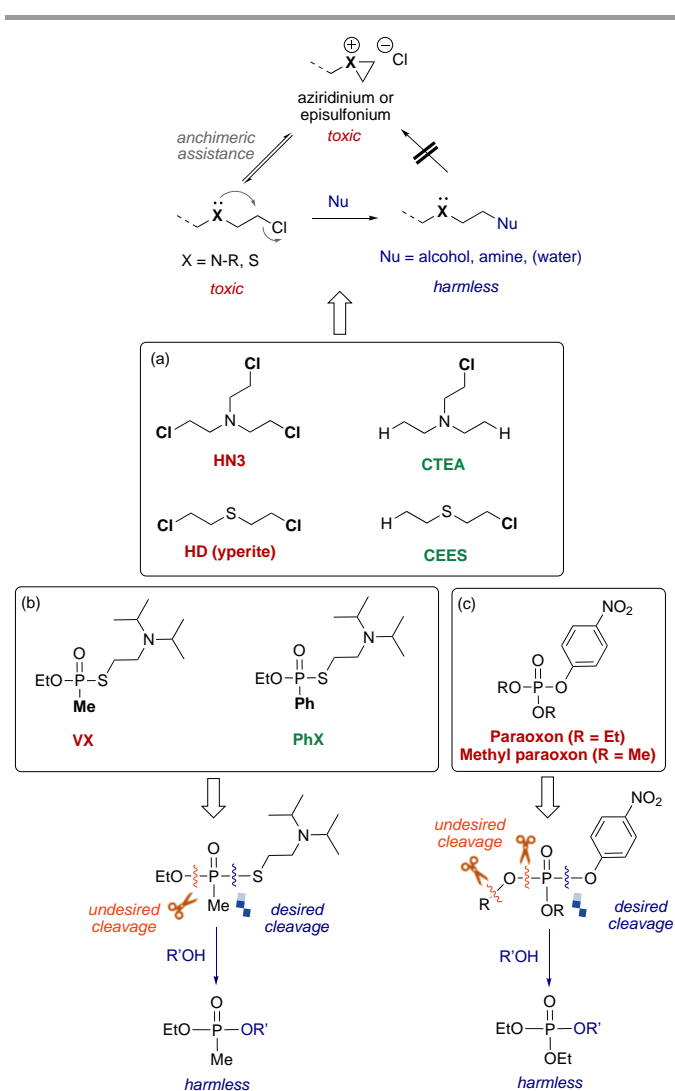
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The neutralisation of structurally varied chemical warfare agent simulants (blister and nerve agents) and pesticides (Paraoxon) with the assistance of high pressure is reported. Chloroethyl amine and sulfide (nitrogen and sulfur mustards), phosphonothioate (V-series nerve agents) and phosphate (pesticide) readily react with simple nucleophilic scavengers (alcohols, amines) at $P > 14000$ bar.

Introduction

In the last decades, an increased global attention has been conducted towards the chemical security and the prohibition of chemical warfare agents (CWAs).^{1–4} Among them, the most common ones are blister agents (sulfur- and nitrogen mustards, HD and HN3) and organophosphorus nerve agents (OPNA), such as the persistent VX. Moreover, some organophosphorus compounds (OPs) are still among the most used agrochemicals in the world, such as Paraoxon (Scheme 1).⁵ The harmful impact caused by such substances on human health and the environment necessitates the development of efficient degradation processes into safe products.⁵ Therefore, there is a growing request to develop new flexible methods for a sustainable neutralisation of chemical warfare agents and pesticides under mild conditions and to ensure effective minimization of toxic products generation.^{5–8} Since the toxicity of these substances is directly connected to their high electrophilicity, the use of water as nucleophilic scavenger of such compounds (*ie* hydrolysis) could look as an ideal detoxification path. Unfortunately, this is a deceptively simple method for several reasons.^{6,9,10}



Scheme 1. Chemical warfare agents (red), pesticides (red), their respective harmless simulants (green), and the corresponding detoxification paths through nucleophilic substitution. (a) blister agents: sulfur mustard HD, nitrogen mustard HN3 and relevant

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simulants (CEES and CTEA respectively); (b) OP nerve agent VX and its simulant PhX; (c) OP pesticides Paraoxon and methyl Paraoxon.

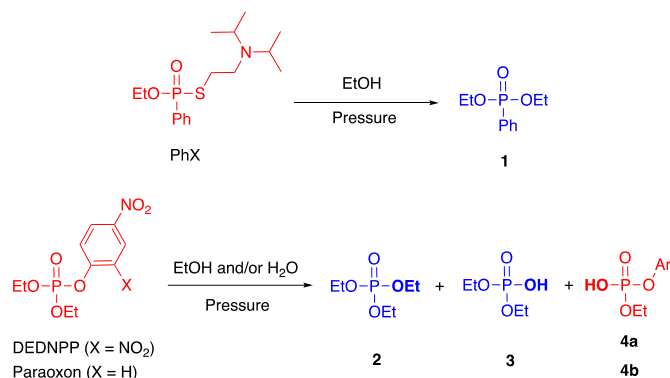
Indeed, yperite HD, which is insoluble in water, reacts very slowly and undergoes partial oligomerization/hydrolysis, rearranging into micelles that still contain important quantities of unaltered yperite in their core;^{11,12} this direct route is therefore little used for mustard agents. Expectedly, this path is also poorly effective for lipophilic OP V-series CWA and phosphate pesticides, which have been precisely designed to resist hydrolysis. For example, Paraoxon exhibits a half-life >20 years in aqueous medium.⁵ Moreover, this reaction must proceed with high selectivity to avoid the formation of still toxic products (Scheme 1). If the insolubility of these harmful molecules can be circumvented by using alcohols as nucleophiles, CWAs are still reluctant to the direct solvolysis and either metal-catalysts or -alcoholates are required for efficient abatement.^{5,6,8,13–15}

Beside the choice of the chemical path, the technology used to perform this detoxification can play a prominent role. Recently, continuous flow reactors have attracted attention as an alternative to classical batch chemistry to ensure rapid and selective neutralization of such harmful chemicals with oxidizing agents.^{16–19} Moreover, successful neutralisation by direct introduction of an aqueous solution of sodium hydroxide in the flow system has also been reported,²⁰ whereas a 3D-printed chemical generator of lithium ethanolate has been later reported as a reliable method.²¹ Importantly, all these methods are not general and each focuses on a specific class of compounds: yperite,^{16,17,19} V-series OPNA,²¹ sulfur-containing CWA,¹⁸ or Paraoxon.²⁰

Regarding alternative technological tools for chemistry, hyperbaric reactors (*ie* affording a pressure of several thousand bars) exhibit several features of high interest in the frame of the decomposition of these toxic chemicals. Indeed, high pressure is particularly well suited to cases where fragile and/or non-reactive reagents/products are needed.^{22–24} High pressures are even used for sterilization in food industry.²⁵ Pressure, like temperature, is a parameter that influences the equilibrium of a chemical reaction and it can be considered as a ‘physical catalysis’ with numerous advantages for the neutralization of toxic chemicals: 1) inert molecules (*eg* for steric reasons), usually become reactive: CWA are highly persistent (*ie* stable) and could thus become more sensitive towards nucleophiles; 2) the involvement of heat-sensitive reagents/products is not a concern: this is of particular interest for CWA since they are often weaponized under gaseous form; 3) the selectivity can be modified since the pressure may allow to obtain compounds thermodynamically less favoured at P_{atm} : in the degradation of CWA, selectivity is essential, since competitive reaction may afford toxic compounds. It is also worth to note that hyperbaric reactors consume energy only during the initial compression step, in contrast to thermal activation with continuous heating. Along these lines, we now report that high pressures promote the detoxification of several categories of OPs compounds (phosphonothioate, phosphate) and blister agents (nitrogen- and sulfur mustards) in the presence of simple nucleophiles.

Results and discussion

Our investigations began with the most relevant analogue of V-series OP: the compound PhX, which keeps all the functionalities of the original phosphonothioate but with reduced toxicity due to the steric hindrance of the phenyl group instead of a methyl (Scheme 2 and Table 1).²⁶



Scheme 2. Reactivity of OP compounds with ethanol and/or water under high pressure: PhX, DEDNPP and Paraoxon

Table 1. Detoxification of organophosphorus compounds: PhX, DEDNPP and Paraoxon^a

| Entry | Substrate | Solvent | P (kbar) | Time (h) | Conv. (%) (1 or 2/3/4) ^b |
|-------|-----------|------------------------------------|--------------------|----------|-------------------------------------|
| 1 | PhX | EtOH ^c | 1·10 ⁻³ | 24 | 1 0 ^d |
| 2 | | EtOH | 14 | 4 | 1 25 |
| 3 | | EtOH | 14 | 24 | 1 53 |
| 4 | | EtOH | 16 | 24 | 1 100 |
| 5 | DEDNPP | EtOH ^e | 1·10 ⁻³ | 24 | 0 |
| 6 | | EtOH | 14 | 24 | 100 (43:57:0) |
| 7 | | MeCN/H ₂ O ^f | 14 | 24 | 100 (0:100:0) |
| 8 | Paraoxon | MeCN/H ₂ O | 14 | 24 | 0 |
| 9 | | MeCN/H ₂ O | 16 | 24 | 35 (0:21:14) |

^a According to Scheme 2. ^b 2/3/4 stands for the detoxification of DEDNPP and Paraoxon. ^c Anhydrous ethanol. ^d At 50 °C, 10% conversion into 1 were observed after 24 h. ^e Commercial ethanol 96%. ^f MeCN/H₂O, 99:1, v/v.

On a formal standpoint, ethanolysis of VX (and its surrogate PhX) allows a specific substitution at the P-S bond that avoids the formation of toxic by-products (Schemes 1 and 2). Unfortunately, as already observed in previous reports, PhX is fully stable in alcoholic solutions under ambient conditions,²¹ and no conversion of PhX into diethyl phenylphosphonate 1 was therefore observed at $P = 1$ bar (entry 1). Even by heating at 50 °C, only 10% of PhX were transformed after 24 h. Since CWAs are often weaponized by spraying (some of them even have high vapour pressure values), the treatment of these toxic chemicals assisted by thermal activation, with the risk of vapour formation, is highly undesirable. Thus, for the reasons cited above, the decomposition of PhX at ambient temperature (20 °C) was assessed in anhydrous ethanol under 14 000 bars (1.4 GPa) in a hyperbaric reactor (entries 2 and 3): at this pressure 25% conversion were obtained after 4 h that increased

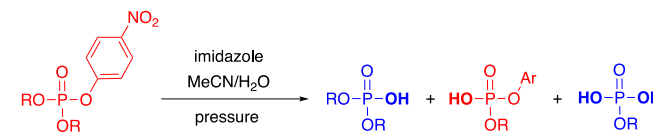
to 50% of conversion within 24 h. Delightfully, increasing the pressure to 16 kbar allowed full conversion of PhX into the desired product **1b** (entry 4). These results clearly demonstrate the benefits of the physical activation by high pressure to perform solvolytic detoxification by nucleophilic substitution with simple ethanol.

Then our studies moved to a more resistant family of OPs: phosphates. Among them, the Paraoxon analogue DEDNPP (diethyl-2,4-dinitrophenylphosphate) is known to exhibit the highest reactivity toward hydrolysis (entries 5-7). In the presence of commercial aqueous ethanol 96%, three products are expected: the detoxified compounds **2** and **3**, corresponding to the substitution of the dinitroaryl group by ethanol and water, respectively. The substitution of one ethoxy group by a hydroxyl group, with the remaining dinitroaryl group would maintain the toxicity (product **4a**). Also, solvolysis with ethanol at ambient conditions proved to be ineffective (entry 5), whereas under 14 kbar a full degradation of DEDNPP into more innocuous ethanolyzed product **2** (43%) and, above all, hydrolyzed compound **3** (57%) occurred in 24 h. Provided that only 4% v/v of water in ethanol was enough to significantly detoxify DEDNPP into diethyl phosphate **3**, the reaction medium was switched to MeCN/H₂O (99:1, v/v). In this new solvent system, we were very pleased to observe a fully selective transformation into **3** at 14 kbar (entry 7). It is worth to note that toxic product **4a** was never observed, and that DEDNPP is known to have a half-life of 56 days in water under ambient conditions.²⁷ Unfortunately, these conditions were not successful with the live pesticide Paraoxon (0% conversion, entry 8). Increasing the pressure to 16 kbar also appeared disappointing since only 21% of the desired product **3** was afforded along with 14% of the toxic aryl alkyl phosphate **4b** (entry 9).

Previous studies proposed imidazole as a nucleophilic catalyst that allows total Paraoxon detoxification in 77 h, in aqueous medium at room temperature.²⁸ Thus, with 6 equiv. of imidazole MeCN/H₂O under 14 kbar, results showed a 95 % conversion after only 24 h into the desired diethyl phosphate **3** accompanied with 5 % of the toxic compound **4b** (Table 2, entry 2). However, we succeeded to improve selectivity of the neutralisation process by increasing the pressure at 16 Kbar and we obtained a 100 % conversion into the innocuous **3** in only 24 h (entry 3). Despite apparent very similar structures, Paraoxon and methyl Paraoxon (diethyl vs dimethyl, respectively) exhibit distinct behaviours. Methyl Paraoxon has a greater tendency to transfer the alkyl group to a nucleophile when compared to (ethyl) Paraoxon. This behaviour was observed in reactions with imidazole, where imidazole selectively attacks the phosphorus atom of (ethyl) Paraoxon and mainly attacks the CH₃ group of methyl Paraoxon.^{28,29} Thus, for methyl Paraoxon, the same conditions afforded as major product the undesired dealkylated product **4c** (44 %), with a mixture of desired diethyl phosphate **3** (30%) along with the over-hydrolyzed and harmless ethyl phosphate **5** (26%). Even after increasing the reaction time at 72 h, the results reminded similar which demonstrate that the reaction had attend its equilibrium at this given pressure. Delightfully, when the

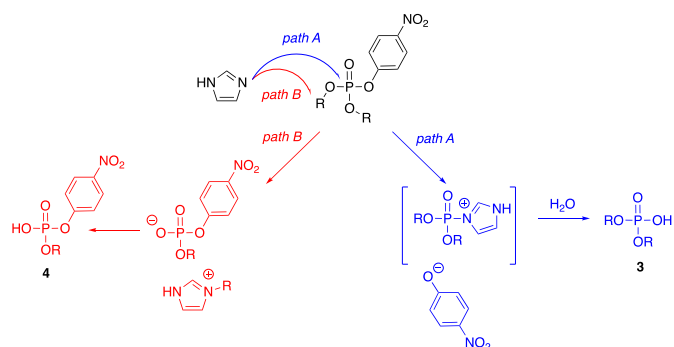
pressure was raised at 16 kbar we succeeded to eliminate the toxic product and obtained a mixture of non-toxic products **3** and **5** at 70 % and 30 % respectively.

Table 2. Paraoxon detoxification under high-pressure with imidazole.^a



| Entry | Substrate | Pressure (kbar) | Conversion (%) |
|-------|-----------------|--------------------|-------------------|
| | | | 3/4/5 |
| 1 | Paraoxon | 1·10 ⁻³ | 0 |
| 2 | | 14 | 100 (95:5:0) |
| 3 | | 16 | 100 (100:0:0) |
| 4 | Methyl Paraoxon | 1·10 ⁻³ | 50 (0:100:0) |
| 5 | | 14 | 100 (30:44:26) |
| 6 | | 16 | 100 (70:0:30) |

^aPerformed in the presence of 6 equiv. of imidazole in MeCN/H₂O, 99:1, v/v.

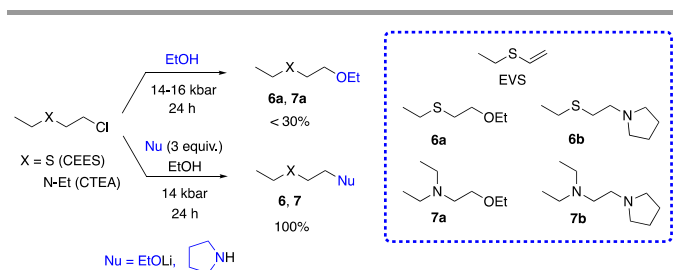


Scheme 3. Decomposition of Paraoxon and methyl Paraoxon in the presence of imidazole.

Mustards agents constitute a structurally different family of compounds. The toxicity of these chloroethyl sulfides and amines (respectively sulfur and nitrogen mustards) also stems from their electrophilicity, albeit with the anchimeric assistance of the S and N atom (Scheme 1).³⁰ These hydrophobic blister agents and their corresponding surrogates (CEES and CTEA, Scheme 1) are poorly reactive in polar solvents as water and methanol. For example, CEES in methanol-*d*₄ undergoes a nucleophilic substitution of the chlorine atom to form 2-methoxyethyl ethyl sulfide with a 50% conversion in 48 h at ambient conditions (still incomplete after 5 days),³¹ whereas a complex mixture of hydrolyzed product and oligomers are afforded in water.¹¹ Based on our success with OP neutralization under high pressure, the direct solvolysis of CEES and CTEA with the environmentally desirable ethanol solvent was attempted under 14 to 16 kbar. Whereas CEES is fully stable

in anhydrous ethanol and exhibit no significant reaction for 24 hours, applying a high pressure only afforded less than 30% conversion into to 2-ethoxyethyl ethyl sulfide **6a** within 24 h, and poor conversion was also obtained with the nitrogen-mustard surrogate CTEA into **7a** (Scheme 4).

A common strategy to enhance the nucleophilicity of an alcohol is to use its conjugate base. Whereas this method was reported to be successful with OP compounds,²¹ century-old reports claim that HD undergoes competitive dehydrochlorination in the presence of an alcoholate, but few details are provided.^{32–34} In our hands, CEES reacted very slowly with EtOLi (3 equiv.) in EtOH at ambient conditions (20 °C, 1 bar) to afford nucleophilic substitution product **6a** (21%) along with <1.5% of ethyl vinyl sulfide (EVS) after 24 h. In contrast, the ethanolysis of CEES under 14 kbar showed full neutralization of the CWA simulant into the desired harmless product **6a** within only 24 h (Scheme 4). Pleasingly, the nitrogen-mustard surrogate CTEA behaved exactly the same way to yield **7a** (Scheme 4).



Scheme 4. Detoxification of blister agents by pressure-assisted nucleophilic substitution

However, in the frame of environmentally friendly process, metal salts could be seen as an issue and neutral nucleophiles could be preferred. In this frame, the aminolysis of mustard agents is an interesting alternative that has been poorly studied. Here also, old reports describe the qualitative formation of the aminoethyl sulfide from HD and amines,^{32,35,36} and more recent works by Bowman-James showed that reacting CEES with Me₂NH (1.25 equiv.) in CDCl₃ by ¹H NMR afforded <10% conversion after 7 days. Whereas these conditions were obviously not optimised to reach the highest conversion (<2 equiv. of amine, apolar solvent), it clearly suggest that the nucleophilic substitution is rather slow under ambient conditions, and hyperbaric conditions could be worthy.³¹ Thus, with 3 equiv. of the nucleophilic pyrrolidine in ethanol at 14 kbar, the expected nucleophilic substitution occurred with CEES, as well as with CTEA (100% conversion in each case), the target **6b** and **7b** as single products.

Conclusions

We have described a straightforward method for the detoxification of structurally varied chemical warfare agent simulants and pesticides in a hyperbaric reactor. Conversely to most neutralization methods that employ corrosive (and possibly explosive) oxidants, this one only involves accessible nucleophilic reagents with no undesirable side effects, nor byproducts with unknown toxicity. Thanks to the high pressure applied (14-16 kbar)

chloroethyl amines and -sulfides (nitrogen and sulfur mustards), phosphonothioate (V-series nerve agents) and phosphate (pesticide) readily react with ethanol, water and amine at P>14000 bar to afford the target harmless compounds with full selectivity. This reaction proceeds smoothly without the need of thermal activation (poorly compatible with chemical weapons because of hazardous vapour emission) and involves inexpensive chemicals (amines in excess being possibly recoverable by acid-base extraction).

Whereas hyperbaric reactors are not yet widely developed in laboratories, these preliminary results highlight the role of pressure as a green and sustainable tool for the treatment of toxic compounds.

Conflicts of interest

There are no conflicts to declare.

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