CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

Destruction and Detection of Chemical Warfare Agents

Kibong Kim,[†] Olga G. Tsay,[†] David A. Atwood,[‡] and David G. Churchill*[,†]

[†]Molecular Logic Gate Laboratory, Department of Chemistry, KAIST, Daejeon, 305-701, Republic of Korea

[‡]Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506-0055, United States

CONTENTS

Received: June 25, 2010
Published: June 13, 2011

dx.doi.org/10.1021/cr100193y | *Chem. Rev.* 2011, 111, 5345–5403

1. SCOPE OF ARTICLE AND PREVIOUS RELATED REVIEWS

This review is shaped in scope by much and various chemical, biological, materials science, device, and chemical engineering literature. This review is intended to make major connections between (i) biological systems, (ii) small molecules, (iii) surfaces, and (iv) micro- and nanoparticles. Important discussion of reports related to organophosphorus pesticides and nerve agent simulants are also included. One main thrust is to approach an *atomic level mechanism*; this is found to be neither well-understood nor well-summarized. This lack of understanding comes mainly from the lack of extensive forays into this research subfield due to the difficulty of working with the extremely toxic live CWAs. Herein, the importance of some older literature, for example, that regarding metal organophosph(on)ate adducts and catalysts from the 1960s, has been included and underscored. This particular material has not been previously reviewed in this context, to our knowledge. We broadly focus on various reports dealing with a sequence of degradations and how these can interface with various aspects of science and instrumentation. Molecular biological aspects are also surveyed. Lastly, biotechnological aspects will begin with earlier microorganism-related work; this will follow with specific enzymes and then with the mention of pertinent protein engineering. However, a mixture of enzymes in one microorganism or a mixture of enzymes give varying results, which creates a challenge for those desiring molecular level understanding.

The nerve agent literature has been reviewed over the years by practitioners of a variety of chemistry-related disciplines that include but are not limited to pharmacology, military warfare, biology, and medicine. Topics of previous reviews include remediation catalysis,[1] agent decontamination,[2] liquid chromatography−mass spectroscopy (LC-MS),[3] AChE reactivation,[4−8] agent detection,[9,10] agent (bio)decontamination,[11−16] agent degradation,[2,17−19] agent destruction,[20] environmental chemistry,[21] agent bioremediation,[22−24] agent biosensing,[23,25,26] preparation of relevant biomaterials,[27] biomonitoring,[28] toxicity,[29−31] solution NMR spectroscopic analysis,[32] surface adsorption,[33] agent derivatization,[34] and agent mimickry.[21] In addition to these reviews, there are also those written for clinical professionals and practitioners in toxicology. Thus, some clear omissions, because of the chemical focus here, include clinical descriptions and the topic of "societal preparation." It is noteworthy to mention AChE enzyme and other inhibitors have been a recent theme in research for treating the symptoms of Alzheimer's disease (AD). There are relatively few organophosphorus-based studies focused on the comprehensive atomic and molecular level chemical sensing and decontamination. A few notable examples can be found, however: It has been 19 years since the *Chemical Reviews* contribution entitled, "Decontamination of chemical warfare agents (CWAs)," by Y. C. Yang and co-workers appeared,[2] and 12 years since their accompanying *Accounts* article, "Chemical Detoxification of Nerve Agent VX."[14] Also, aspects of organophosphonate detoxification centered on the utility of hypervalent iodine were published in *Chemical Reviews* in a 2002 article titled, "Phosphorolytic reactivity of *O*-iodosylcarboxylates and related nucleophiles."[35]

Research articles dealing with organophosphonates also sometimes include mention of mustard (H-type) agents. The mustard bis(2-chloroethyl) sulfide ($C_4H_8Cl_2S$), for example, is a cell poison. Thus, these types of compounds lie outside the scope of this review. For a review of mustards and some leading pertinent references, see, for example, the B. M. Smith review[1] and other sources.[36]

2. INTRODUCTION

Nerve agents are considered the most nefarious of synthetic chemical derivatives. They are potent acetylcholinesterase (AChE) active agents, clearly differentiated from other chemical warfare (CW) type agents (blister, blood, choking, incapacitating, tear (lachrymating), and vomit agents) because of their phosphorylating mode of action, derived from their organophosphonate structure (RO(O═P(R′)OR″). Specifically, this unique structure is the key to its danger expressed by mammalian toxicity compared with similar related species (*vide infra*). Nerve agents and pesticides comprise phosphorus(V) compounds with a terminal oxide and three singly bonded substituents (two alkoxyl and one alkyl group) (Figure 2) and are derivatives that have inspired a wide variety of studies into their convenient detection and detoxification; these studies are embodied in this review. We want to connect different subdisciplines in a cross-cutting molecular scale approach for chemists, biologists, materials scientists,

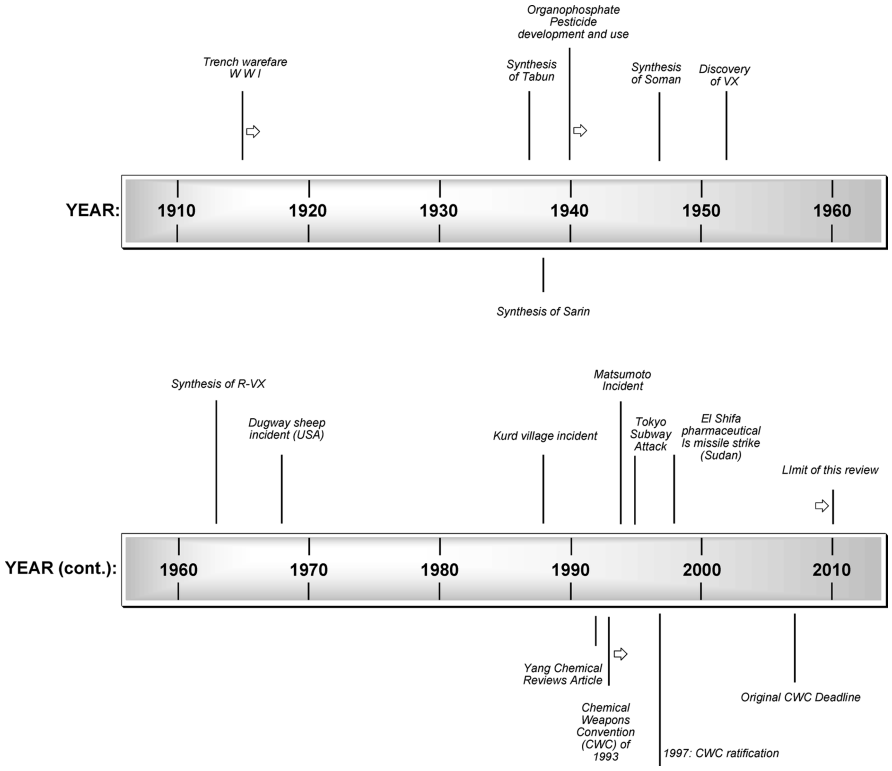


Figure 1. Graphical timeline of notable nerve agent incidents and related dates.

practitioners of nanotechnology, and possibly even medical personnel and physicists as well as some nonscientists. There is a focus on metal-containing systems and related studies herein because of the utility of metals in achieving selective and low-temperature degradative processes and selective sensing. These reports also extend to main group chemistry such as various reactive oxygen species, as well as halogens such as iodine. Metals allow for only one way of sensing, so we will broaden our approach to larger swaths of the periodic table. Whether considering metals or not, the importance of thinking on the molecular/atomic level is an important undertaking in attending to the chemical descriptions delineated in the Chemical Weapons Convention (C.W.C.). There are inextricable links between contamination and sensing. Importantly, when agents are decomposed, *their downstream components must be monitored* to confirm the absence of the agent or how much hydrolysate has been produced.

2.1. Destruction

Due to the latent dangers of CWA nerve agent species that exist when stockpiled, adequate destruction capabilities are required. We will focus on simple hydrolytic processes first. Then, we will introduce metal-containing systems that are important in catalysis. We will detail the main modes and systems of decontamination.

2.2. Sensing

There is also a need to have adequate agent sensing[37] and monitoring to allay the fear that a rogue entity can (synthesize agents and) disperse them in a surprise attack threatening civilian populations. An ideal sensor in this context is considered as, but is not limited to, a well-defined, reliable, and reusable (sensor-to-sensor reproducibility) system that possesses various and distinct attributes that include high analyte sensitivity (i.e., ideally part(s) per trillion (ppt) sensitivity), selectivity (against interfering species), adequately short response time, low false alarm rate, low cost, and tolerance to a realistic range of temperatures. It is also important to maintain consistent operation and have a lengthy shelf life (resistance to aging) and steady lifetime reliability. Reports will be ordered with respect to technique or mode of sensing. Many of these criteria will be touched on. Importantly, many of these issues relate to rational ligand design as well as careful and creative research undertakings. Regarding metals, *d*-block metal chemistry will be introduced for catalysis and more. Particularly, adequate control of complex color, electronics, sterics, and molecular geometry and reversibility can be easily achieved through transition metal chemistry,[38] and these criteria relate to the requirements for sensors.

Having underscored points of sensing and decontamination separately, it is now important to establish certain ties between them. Herein, we will however downplay the separate profile of pesticides; pesticides will be mentioned alongside nerve agents where they give particular insight into agent behavior. They exist on a "toxicity continuum". Notably, at the end of our review we try to critically evaluate the current state of the art. This perspective is meant to give the researcher the best vantage point in starting their future studies. This review is relevant to primary literature that has appeared in a print or online form through 2010.

CAUTIONARY NOTE: Conducting new or repeating old experiments with particular organophosphonate-based compounds, for example, actual or "live" organophosphonate-based nerve agents, must be performed by properly trained personnel (supervision) only, at specialized facilities (e.g., Aberdeen Proving Grounds) under only genuine and adequate safety precautions. The use of proper training, preparation, and common chemical sense derived from formal

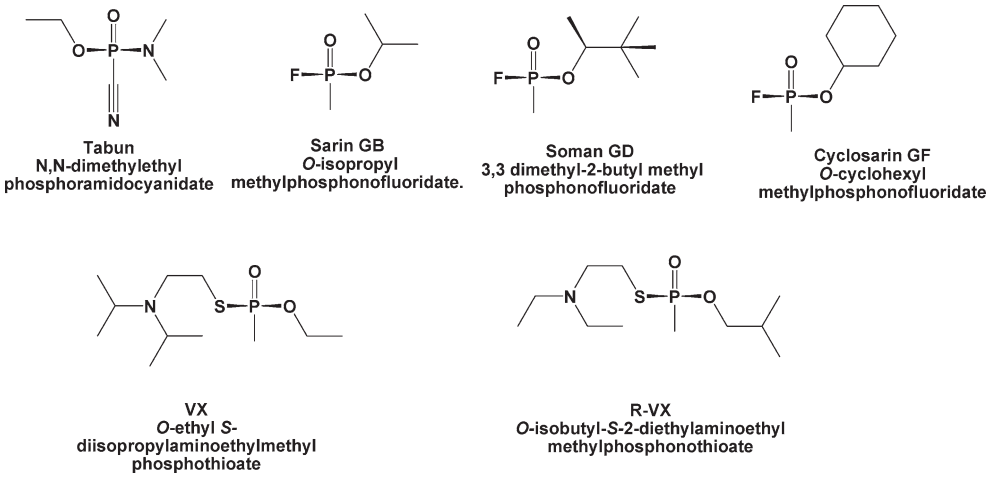


Figure 2. Structures and names of G-type and V-type agents (in order of discovery). Agents shown as *S*-stereoisomers.

training is especially applicable here as it is with any chemical laboratory research.

2.3. Historical Context

2.3.1. Brief History and Molecular Structure. The pragmatic use of certain kinds of chemical-based deterrents (e.g., smoke clouds, arsenic-based fumes, etc.) during human battlefield combat goes back millennia and is often reflective of the technical and experimental sophistication of the society and point in time. There has been a definite progression in the development of dispersible chemical media in human warfare in the past century guided by the knowledge of synthetic chemistry (see the timeline in Figure 1). The replacement of chlorine (Cl_2) by phosgene ($COCl_2$) and then by mustard gas reflects an increasing sophistication directly reflecting greater chemical and scientific understanding. Such techniques in *modern* battle circumstances can be considered to originate from the tactics used in trench warfare (Ypres, Belgium) during World War I. At Ypres, Belgium, chlorine-containing compounds were used effectively and gas warfare accounted for ~91 000 deaths (~1.3 million casualties) overall.[39]

The exact history of the development of nerve agents[40] is not evident when surveying the primary chemical literature. Such development was tied to secretive late 1930s and early 1940s wartime efforts that begot substances that were subsequently known as the G-type (German-type) nerve agents and related compounds (Figure 2). G. Schrader and co-workers associated with I. G. Farbenindustrie (Leverkusen, Germany) prepared tabun in 1936. Subsequently, sarin (1938) and then soman (1944) were prepared. These compounds were manufactured in the thousands of tons. Cyclosarin was later developed in 1948. These compounds were known openly to the greater world after the end of WWII.[41]

An even more perilous extension to this secretive work was conducted in Great Britain in Porton Down where VX (ethyl *S*-diisopropylaminoethyl methyl phosphothioate), the first member of the V-class (venom or venomous-type) was prepared in the early 1950s. This work was part of an ICI patent application and thus was registered in the patent literature before scientists at Bayer (Germany) were able to do the same. Scientists in Great Britain discovered V agents while synthesizing new insecticides. Russian scientists later prepared the R-VX analogue in 1963, a constitutional isomer bearing diethylamino and isobutoxide units (Figure 2). The production of these compounds continued during the Cold War leading to the present day stockpiles of arsenals (munitions, shells) in various quantities that remain stored in military depository locations in mainly the U.S. and former Soviet Union (*vide infra*). In recent years, the status of these stockpiles has been monitored by news agencies, as the efforts for decontamination are enhanced.[42]

While the known nerve agents are closely related [$O{=}P^{V}(OR)$]-containing species (Figure 2), they do have some important differences. In addition, all except tabun [$(EtO)O{=}P(-CN)(NMe_2)$][43] contain a P-CH_3 group. Thus, with this exception, the [O=P-Me] fragment is a ubiquitous nerve agent moiety. Sarin, soman, and cyclosarin[44] are all closely related fluorophosphonates (P*H* → P*F*). In the short V-series, there exist VX[45] and isomer R-VX, which possess the pendant amino group an additional sp^3-hybridized group 15 center. Chinese VX involves a butoxy group compared with R-VX.[46] The V-class gives rise to more complicated decomposition chemistry and sensing protocols (*vide infra*). Phosphorus(V) is essential; there are no P^{III} species/intermediates known at any stage, except perhaps as putative species in high temperature surface chemistry.

2.4. Related Compounds and Nomenclature

2.4.1. Phosphorus(V) Parent Compounds, Fundamental Chemistry. The complexity of agent substitution and naming of compounds can be alleviated by reference to simpler parent molecules. A presentation of simple phosphorus(III) and (V) hydride, hydroxide, and oxide compounds and their names is given in Figure 3. Here, acidity values as pK_a's are provided. All nerve agents take their names from the phosphonate class. The simplest phosphorus analog is PH_3. This homoleptic trivalent hydride can be formally substituted by hydroxyl groups to give phosphinous acid [PH_2OH]; a second hydroxyl group affords phosphonous acid [$PH(OH)_2$], and finally phosphinic acid [$P(OH)_3$]. Phosphinous acid and its derivatives are unstable in relation to the tautomeric form, phosphine oxide ($O{=}PH_3$), which predominates due to its strong P=O bond.[47] The only known example of the stable phosphinous acid is $(CF_3)_2POH$.[48] Phosphonite species formally lack the phosphoryl oxygen [P=O].[49] Related pentavalent phosphorus species include simple phosphine oxide ($O{=}PH_3$). $O{=}PPh_3$ and related species can give structural insights into sensing and decontamination of OPs, but their hydrolysis chemistry would clearly differ in that P−R

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

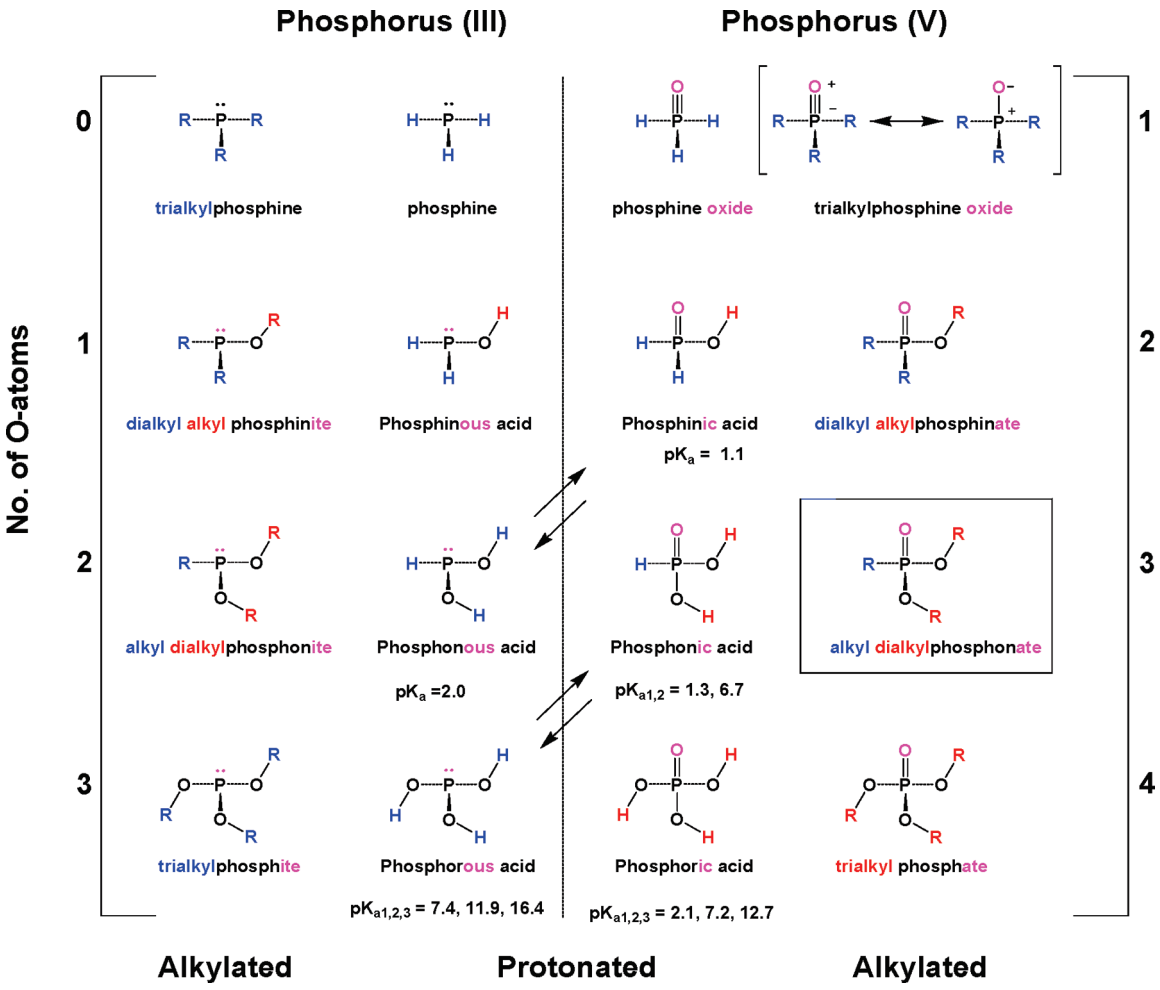


Figure 3. Structures and names of the rudimentary, mononuclear three-[53] and five-valent phosphorus hydrides, hydroxides, and oxides.

bonds are very stable against bond rupture. Formal incorporation of additional oxygen atoms gives phosphinic acid ($O{=}PH_2OH$) and phosphonic (phosphorus) acid [$O{=}PH(OH)_2$]. Notably, these species may tautomerize between P(V) and P(III), that is, $H_2P(O)OH$ to $HP(OH)_2$ (Figure 3). Also a tetrahedral structure [$O{=}PH(OH)_2$] is more stable than its isomer phosphonic acid, $P(OH)_3$. This form can be stabilized by coordination with some metals.[50] There are also other related simple phosphorus-containing species. A variety of other cyclic and chain phosphorus oxyacid derivatives exist as well (e.g., orthophosphate [$^{2-}O_3P{-}O{-}PO_3^{2-}$]).[51] Arsenic analogs may also possess toxicity.[52] Phosphorus sulfides are also important in this context because of intermediates involved in nerve agent (NA) synthesis. P−F and other halide species and their chemistry are also relevant.

2.4.2. Pesticides. The ability of man to dispose of *pests* (i.e., mainly insects) by chemical means may predate his like ability to dispose of or incapacitate his fellow man. Thus, taking roughly the same post-WWI time frame, organophosphates (phosphorus triesters) were developed (Figure 4). The preparation of pesticides[54] is entwined with that of the nerve agents since they possess similar structural features and formulas (Figure 4). These species possess the same mode of action (*vide infra*) as nerve agents and are on the "toxicity continuum" but are less hazardous. Prior to the 1930s, pesticides took the form of chlorinated organic compounds. As with related chemical warfare developments, chlorine-containing pesticide compounds eventually gave way to phosphorus(V) compounds. A discrete period of heavy rational development of organophosph(on)ate-based pesticides (insecticides) after World War II (1940s−1950s) spawned a number of new related species. Well-known chemicals of this type are almost always referred to by their common or industrial names, for example, (alphabetically) chlorpyrifos, coumaphos, cyanophos, demeton, demeton-S-methyl, diazinon, dichlorvos, dioxathion, glyphosate, fonofos, malaoxon, malathion, methamidaphos, mevinphos, oxydemeton-methyl, paraoxon, and parathion (Figure 4). Whereas pesticides are less immediately toxic (to AChE) per the known LD_{50} values in nonhuman model systems when compared with nerve agents, their heavier use and looser monitoring is perhaps cause for greater concern. Pesticides sometimes possess a terminal sulfido group [P═S]. This alters the physical properties (i.e., hydrogen bonding, *vide infra*) and has ramifications for every application. Having said all this, Monsanto's Roundup herbicide (Figure 4) is an example of a phosphonate that is relatively nontoxic to humans and degrades easily in soil.[55]

2.4.3. Simulants. Due to the grave toxicity of the nerve agent class, various comparatively innocuous and readily available molecules are frequently used in "nerve agent" research. These simulants (aka, surrogates or mimics) exist in the "continuum" of

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

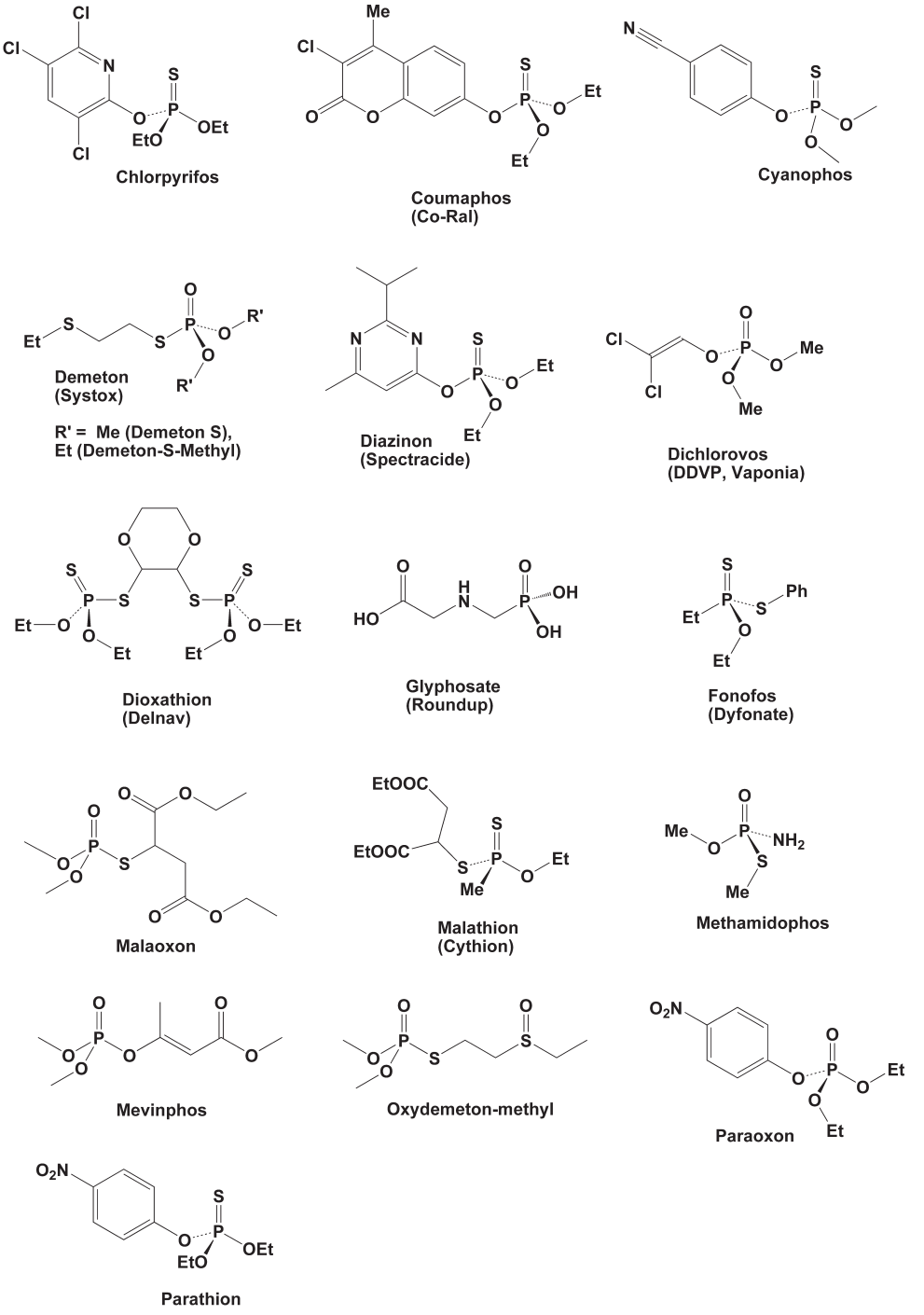


Figure 4. Structures and names of selected relevant organophosphate-based pesticides.

lowered AChE toxicity from the agents. They are typically less expensive as well. These help in less vigorous laboratory settings when testing a new chemical system for NA detection or decontamination capability. The structures of various simulants appear in Figure 5, and interestingly, some may also not be phosphorus-containing (Figure 6). A NA simulant could be a known pesticide (Figure 4). The utility of these in research will be mentioned throughout this review. Importantly, simulants provide an *incomplete measure of utility*, never exactly the same behavior as with actual "live" agents. For instance, in terms of VX chemistry, none gives "the unique intramolecular amino nitrogen effect in VX."[14] In some molecules, the chemistry at phosphorus is maintained, but few of these closely resemble the thiocholine moiety, which alone is an essential degradation product in the reaction, see Schemes 1 and 2. They are mainly P(V) centered, and many possess one or more alkoxyl groups.[56] DMMP is, by far, the work-horse in nerve agent-like investigations.

2.4.4. Decomposition Products. Nerve agents and pesticides produce some common signature byproducts upon hydrolysis (Scheme 1). All species except tabun give the all-important methylphosphonic acid (MPA). The hydrolysis of tabun may give [O═P(CN)] and dimethylamine or nitrile. The hydrolysis

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

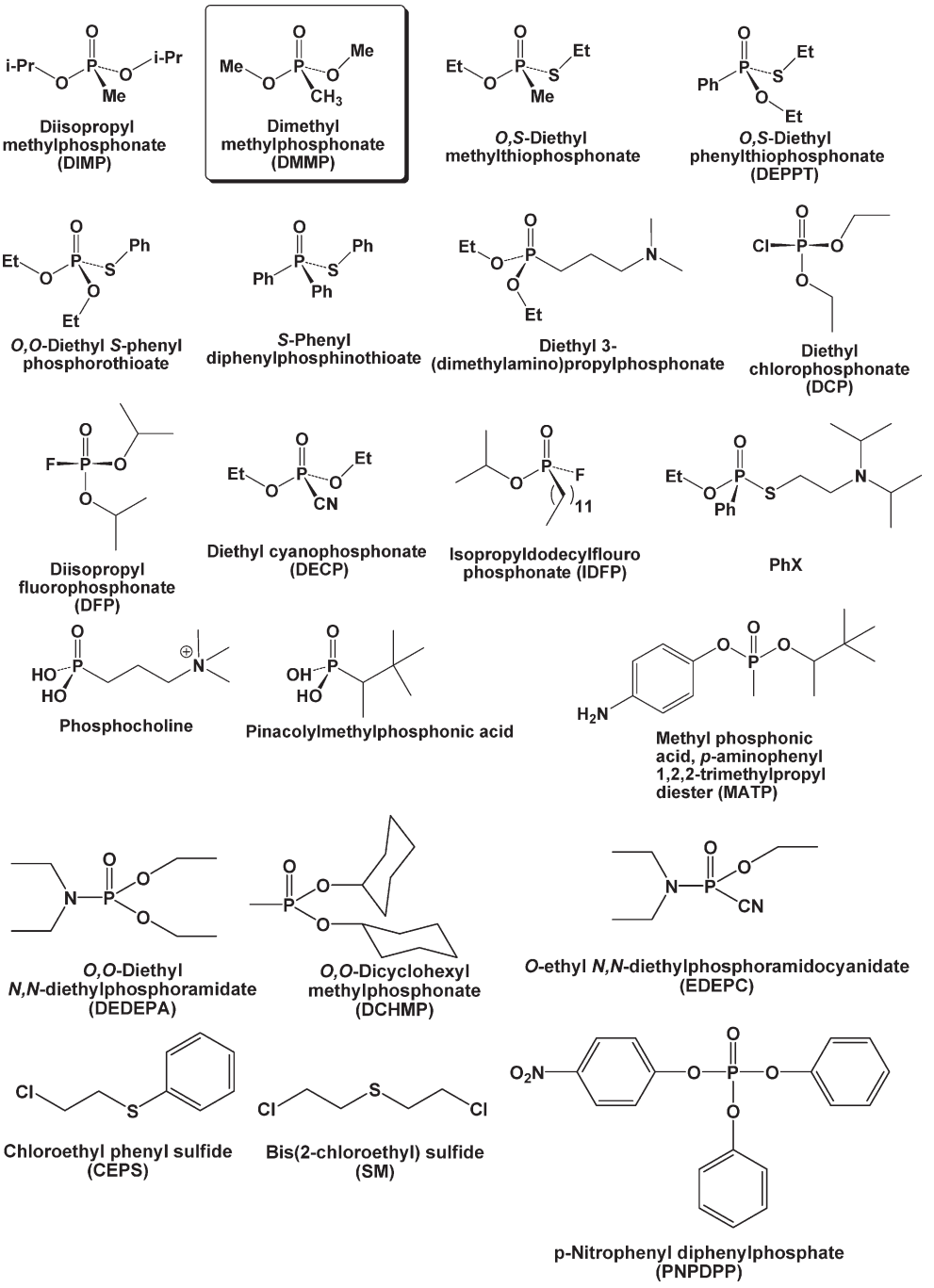


Figure 5. Structures and names of some relevant mimics used in sensing as mimics for sarin, VX, etc.

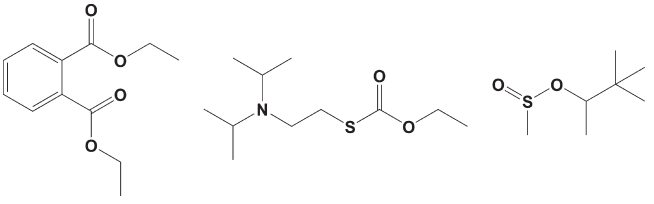


Figure 6. Some non-phosphorus-containing mimics and interferants.

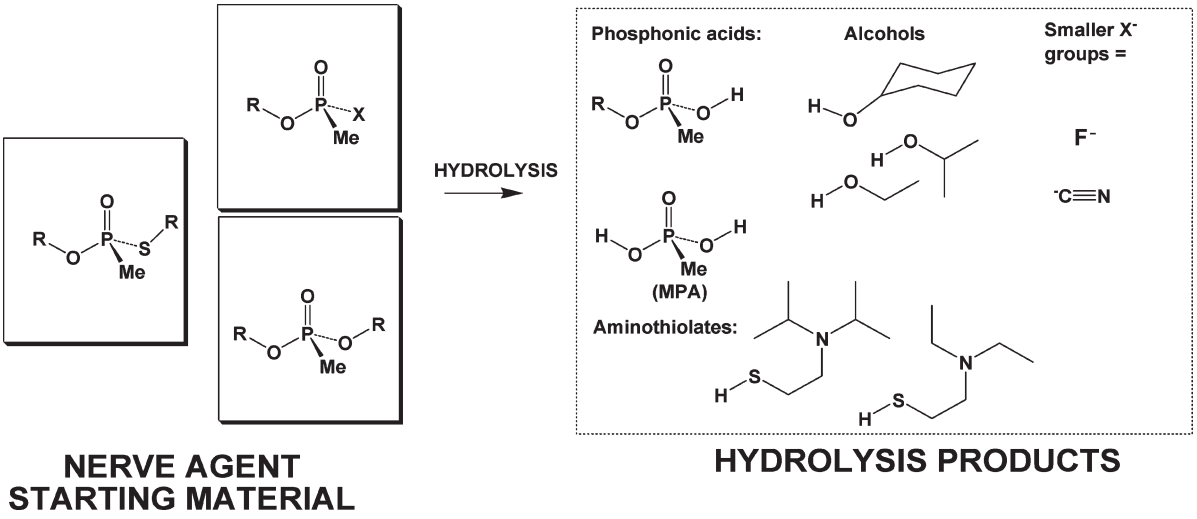
of sarin, soman, and cyclosarin, in addition to giving F^-, may also give the respective alkoxides or alcohols: isopropoxide, picolyl oxide, and cyclohexyl oxide.

2.5. Toxicology

2.5.1. Acetylcholine Esterase (AChE) Inhibition. Acetylcholinesterase (AChE) inhibition is the most well-known mode of action of nerve agents. Inhibition occurs through the irreversible binding of organophosphates to the catalytic site of the enzyme.[57−59] Acetylcholinesterase (AChE) is an enzyme that hydrolyzes the neurotransmitter acetylcholine (ACh) in postsynaptic membranes and neuromuscular junctions. When nerve impulses reach a nerve ending, acetylcholine is released from the terminals of presynaptic nerves into the synaptic or neuromuscular junction and binds to the ACh receptor site on the postsynaptic membrane, thereby causing stimulation of the nerve

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Scheme 1. Generalized Hydrolysis of Nerve Agents



fibers or muscles. AChE serves as a regulator of neurotransmission by ACh hydrolysis. Enzymatic hydrolysis involves nucleophilic addition and acid-based reactions at the catalytic site of the enzyme that involves a catalytic triad (three amino acids, serine, glutamic acid, and histidine) (Scheme 3).[60]

Acetylcholine and the enzyme form an enzyme−substrate complex by electrostatic attractions between the positive charge on the acetylcholine nitrogen and the negative charge in the acidic site. Then the imidazole moiety of the histidine catalyzes acetylation of the serine hydroxyl group; the acetylated enzyme then allows for nucleophilic attack by water to occur. The deacetylation reaction results in the free enzyme and release of inactive choline and acetic acid. Catalytic activity of AChE is very high with a turnover number of $>10^4$ s^{-1}.[61]

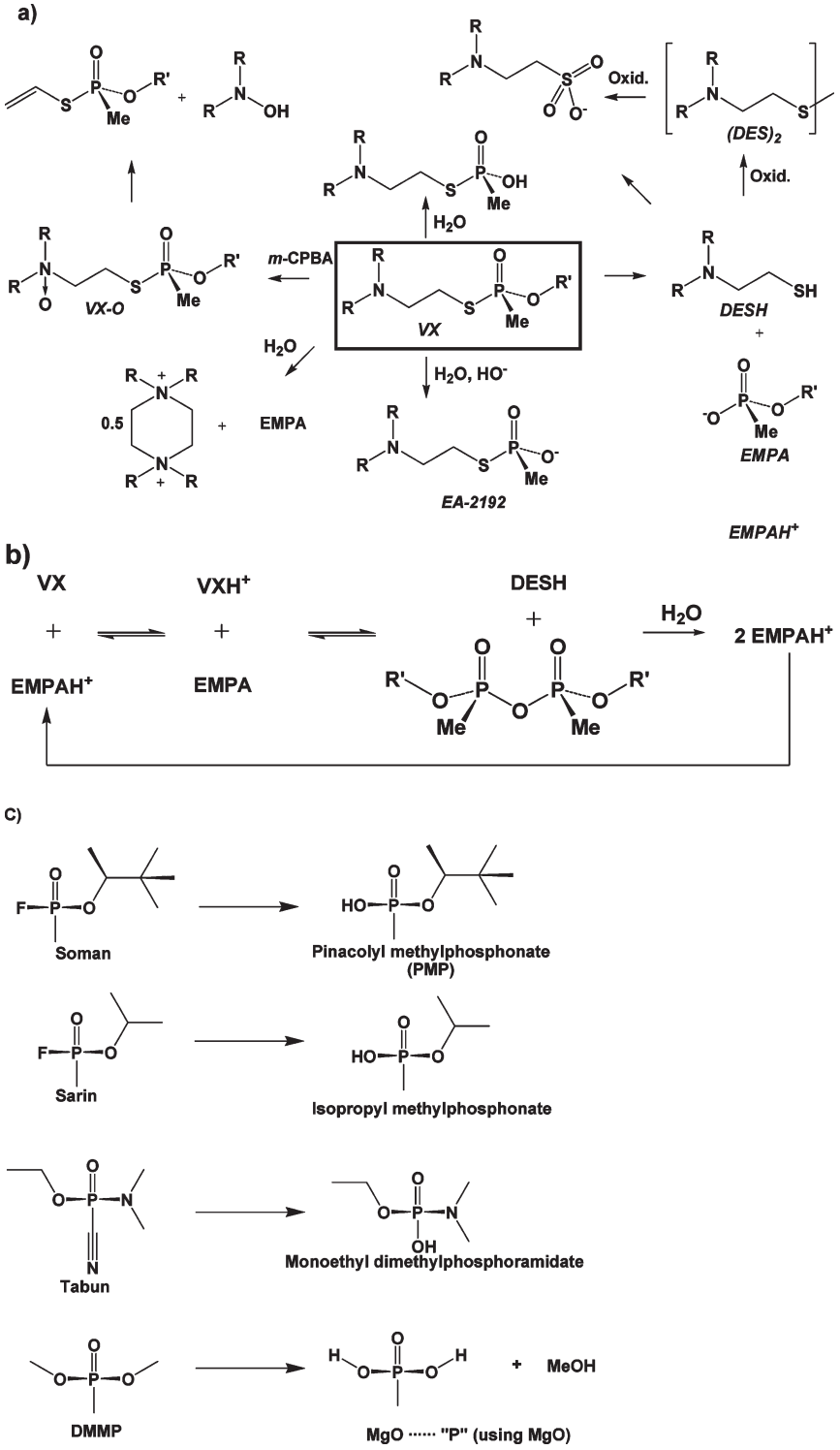
The mechanism of AChE inhibition with organophosphates is analogous to the reaction of enzyme with ACh, except for the reaction in which the leaving group of the organophosphates is lost, so the enzyme becomes phosphorylated instead of acetylated (Scheme 4).[62,63] Theoretical investigations show that phosphorylation is a two-step addition−elimination in which the addition step is rate-determining, while the elimination process is faster. It should be noted that phosphorylation occurs via a trigonal bipyramidal intermediate, whereas in the case of acetylation, the carbonyl carbon is expected to pass through a tetrahedral intermediate.[64−66] The irreversibly inhibited phosphorylated enzyme can no longer hydrolyze acetylcholine. This leads to an accumulation of acetylcholine in cholinergic receptors and consequent continuous stimulation of the nerve fiber.

Phosphorylated AChE is stable but can undergo a possible secondary process. The first one is the reactivation−hydrolysis of phosphorylated enzyme. But the rate of hydrolysis is much slower than in the case of an acetylated enzyme.[63] Another mechanism is the breaking of the PO−C bond in the inhibited enzyme. This reaction is known as "aging".[67,68] Through this reaction, the enzyme cannot be reactivated, and inhibition is completely irreversible. In the case of tabun-treated AChE, aging occurs through agent P−N bond scission.[69,70] But an alternative mechanism has also been proposed and is shown in Scheme 5.[71]

All known nerve agents possess a stereogenic phosphorus. Interestingly, soman possesses one additional stereocenter on the carbon of the pinacolyl group. These stereoisomers react with acetylcholinesterase at different rates resulting in different toxicological properties.[31] Through the measurement of the bimolecular rate constant of inhibition of AChE with the stereoisomers, and their LD_{50} levels on mice, it was established that for soman and sarin, the rates of inhibition of AChE by the P(+) isomers are 3−4 orders of magnitude less than those for the P(−) isomers; LD_{50} values of the P(−) isomers of soman are much lower than those of the P(+) isomers. The configuration on the carbon atom in soman does not have much influence on the rate of "aging".[72] For tabun and VX, the rates of inhibition of AChE by the (+) and (−) enantiomers differ by 1−2 orders of magnitude. For both agent forms, like for soman, the (−) enantiomers with a higher rate constant also have a lower LD_{50}, 119 μg/kg and 12.6 μg/kg for tabun and VX, respectively. But the difference is not as dramatic as for the soman stereoisomers.[31]

2.5.2. Endocannabinoid System Activation. Acetylcholinesterase is a primary target for nerve agents; however, some of the pharmacological effects of organophosphates cannot be explained only by inhibition of cholinergic activity.[73,74] Thus, the endocannabinoid system is a possible noncholinergic target. In fact, there may be many as of yet unknown systems impacted. Cannabinoids (CBs) (Figure 7) can reduce the amounts of conventional neurotransmitters such as acetylcholine through a retrograde signaling pathway.[75] In this process, the retrograde neurotransmitter is released from the postsynaptic cell and binds into receptors on the presynaptic cell, while the conventional neurotransmitters such as acetylcholine, travel from the presynaptic cell and activate receptors on the postsynaptic cell. Activation of the cannabinoid receptors temporarily reduces the amount of acetylcholine produced. Several studies suggest that some organophosphonates can bind directly to components of the cannabinergic signaling pathway, such as to CB1 receptors, fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase (MAGL).[76−78] For example, it was reported that nerve agents such as the sarin homologue isopropyldodecylfluorophosphonate (IDFP) (Figure 5) and the insecticide metabolite chlorpyrifos oxon (CPO) induces cannabinoid behavioral effects resulting in a greater than 10-fold increase in brain level concentration of endocannabinoid resulting in the complete blockage of their hydrolytic enzymes.[79] Paraoxon (Figure 4) inhibits FAAH activity and blocks agonist binding at the CB1 receptor.[80] These results suggest that organophosphorus agents

Scheme 2. Some Important Hydrolytic and Other Pathways for V-type Derivatives



can induce noncholinergic toxicity through hyperstimulation of the endocannabinoid system.

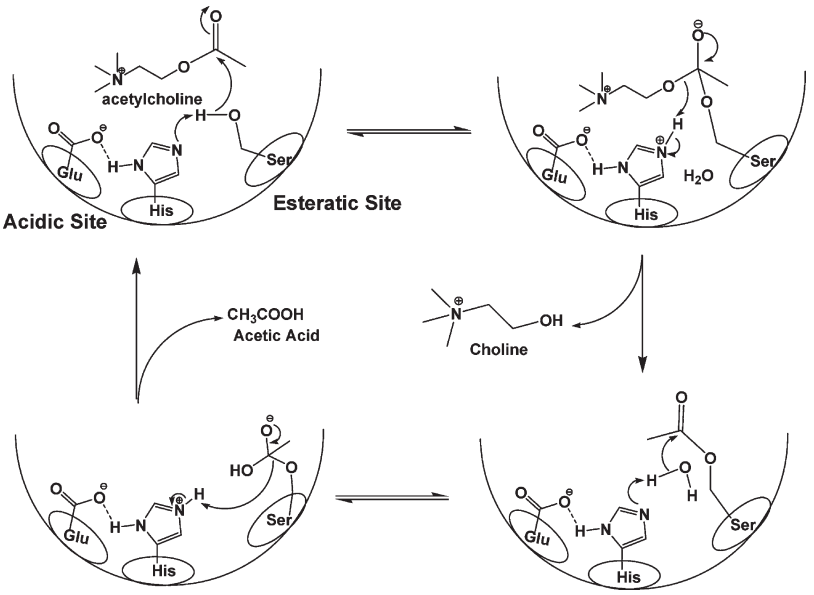
Other neurological systems and biomolecules can be targeted as well.[81,82] It was reported that organophosphorus agents chlorpyrifos and chlorpyrifos oxon react with tubulin protein in disrupting microtubule structure. Organophosphorus agents phosphorylate tyrosine and serine residues in β-tubulin.[81]

2.6. Critical Needs To Decontaminate and Detect

The unanticipated terrorist use of deadly chemical agents in the past 30 years during complete or relative times of peace has caused a malease that exists to the present day. These previous events are widely publicized but are also tied to reports in the primary chemical literature. Villages in Iraqi Kurdistan were the sites of nerve (and mustard) agent use in 1988 during the

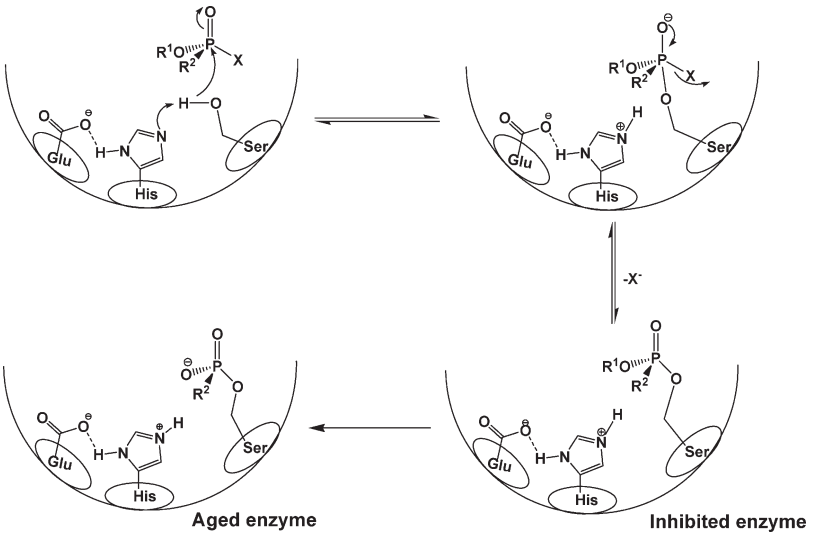
dx.doi.org/10.1021/cr100193y |Chem. Rev. 2011, 111, 5345–5403

Scheme 3. Acetylcholinesterase Hydrolysis of Acetylcholine [a]



[a] Adapted from ref 60.

Scheme 4. Inhibition and "Aging" of AChE with Organophosphates [a]



[a] Adapted from ref 60.

Al-Anfal campaign leading to thousands of deaths.[83,84] Then, there were several *urban* events in Japan perpetrated by the Japanese Aum Shinrikyo cult. These included (i) a release of sarin in Matsumoto, Nagano (June 1994), in which ~7 people were killed and >200 were injured, (ii) isolated assassination(s) (attempts) during 1994−1995,[85,86] and (iii) the City of Tokyo (Japan) subway attack in March 1995,[87] standing as the most widespread "terrorist" NA use (12 dead, ~5000 injured). More than 100 000 U.S. troops may have been exposed to the sarin and cyclosarin in Khamisiyah, Iraq, during the Gulf War in 1991.[88] More recently, there was also the use of a sarin-filled artillery round against coalition forces during the second Gulf war in Baghdad, Iraq, in May 2004.[89,90]

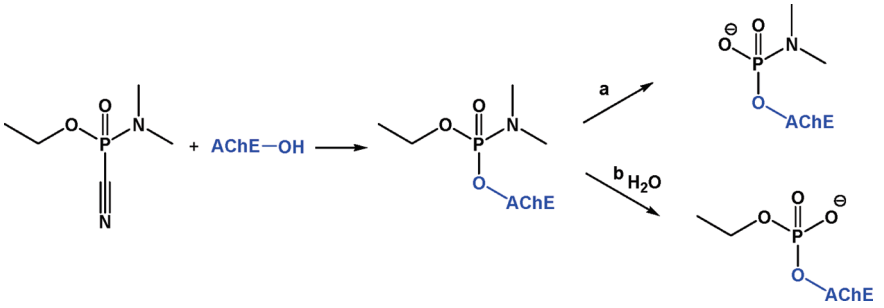
In the United States, false positives such as the one in Washington DC in February 2006[91] for VX exposure have raised questions about the reliability of sensors and the public readiness for future agent-related attacks. Extremely preemptive means have at times also led to controversy: the fear of covert manufacture of CWA's led to a military strike by the U.S. on the El Shifa Pharmaceuticals manufacturing facility in Khartoum, Sudan, in 1998 on the suspicion that organophosphonate nerve agents were being produced there.[92] Thus, good sensing technology may guide sound diplomacy as well.

2.7. Treaties and Conventions

The level of world stockpiles of organophosphonate nerve agents are significant, especially those in U.S. and Russia. The

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Scheme 5. Mechanisms Proposed for "Aging" of Tabun through (a) C−O Bond Cleavage and (b) P−N Bond Cleavage



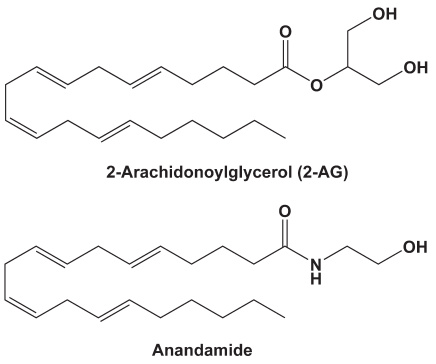


Figure 7. Structure of two endocannabinoids that participate in the retrograde signaling pathway.

stockpiles are being reduced as countries attempt to abide by the contractural agreement set by the Chemical Weapons Convention of 1997 (drafted, 1992; signed, 1993; effective 1997).

3. STOCKPILE DESTRUCTION

3.1. Agent Storage

Chemical agents can be stored either in bulk quantities or in munitions. Agents stored in bulk are typically contained in large cylindrical ton containers, similar to those used for storing or shipping many commercial chemicals. These more innocuous containers exclude explosive devices and fuel assemblies. Other repositories of nerve agents are in munitions: land mines, rockets, artillery projectiles, and mortar projectiles. Some munitions have no explosives or propellant, whereas others contain some combination of fuse, booster, burster, and propellant, which are sensitive to detonation. Many but not all stockpiles are stored in "igloos" (earth-covered bunkers).

3.2. Protection Protocols and Logistics

Any direct human handling of nerve agents and materials contaminated by them constitutes a high health risk due to extremely high toxicity of the agents (see above). Monitoring of the workplace environment and occupational health programs are needed and developed.[93] Chemical monitoring of air, liquids, and solids must be provided by proven systems such as the automatic continuous air monitoring system (ACAMS) and the depot area air monitoring system (DAAMS), mass analysis, and chromatography.[93] Employees must be provided with personal protective equipment and be extremely well-trained. Personal protection devices may include respirators, safety glasses, earplugs, and earmuffs. Detailed decontamination materials and methods are described elsewhere (section 5).

The first step in the destruction process is the actual transportation of weapons or ton containers from the storage place to the destruction facility. It is obvious that this step is associated with high environmental risk and public discontentment and is always considered seriously. The characteristics of weapons and containers, characteristics of the packaging, type of transport vehicles, and external factors such as the possibility of accidents and the venue of transportation are considered in evaluation of transportation risk.[94] In Russia, public opposition to the transfer of all chemical agents from any storage site to one central disposal plant forced the government to build "on-site" destruction facilities at six of its seven storage sites. In the U.S., transportation of dangerous weapons also raises major public concern. Nowadays, destruction facilities are on-site, located at existing storage sites.[95,96]

3.3. Background

Before the Chemical Weapons Convention, dumping of wastes at sea was a simple approach for "destroying" munitions and materials remaining after the First and Second World Wars. In the Baltic sea, drums of waste were often encountered by the fishing industry.[97] The last sea-dumping case was operation CHASE in the Atlantic Ocean during the 1970s carried out by the U.S. Army.[98] Waste burning in open pits and burying were also pursued as alternative disposal methods. In the case of burying, very slow containment corrosion and subsequent slow release of toxic compounds lead to localized contamination of soil and groundwater, and thus it represents long-term environmental threats. Also, both sunken and buried munitions might explode causing a possible sudden release of nerve agents. In 1969, the National Research Council (NRC, U.S.) decided to end the sea-dumping method. Other disposal technologies were studied, and many technologies are still under consideration and are presently in different stages of realization.[99−101] Russia has developed its own two-step process involving neutralization and detoxification with a cocktail of organic compounds. This mixture is then combined with bitumen, sealed in drums, and buried.[96,97] Currently, the U.S. Army employs technologies that include thermal processes such as classical incineration as well as hydrolysis with supercritical water oxidation.

3.4. Methods Currently Employed

3.4.1. Incineration. In 1982, the NRC endorsed incineration technology as the recommended method. It is known as the "baseline" system. The first full-scale prototype facility using this system is the Johnston Atoll Chemical Agent Disposal System

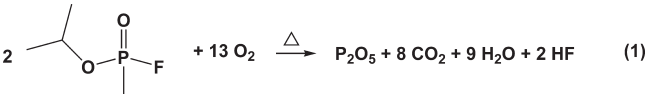
dx.doi.org/10.1021/cr100193y |Chem. Rev. 2011, 111, 5345–5403

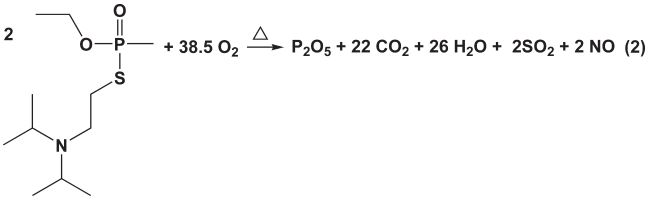
(JACADS); its construction began in 1985, with Operational Verification Testing (OVT) being conducted from 1990 to 1993. This technology was quite effective for destroying stockpiled warfare agents and is currently widely used in Germany and the U.K. and by the U.S. Army.[102]

In addition to the JACADS in the Pacific, there are eight chemical weapons stockpiles within the continental U.S. at Army facilities: Anniston, AL, Pine Bluff, AR, Tooele, UT, Umatilla, OR, Aberdeen, MD, Newport, IN, Richmond, KY, and Pueblo, CO. Nowadays, incineration technology is employed at Anniston, Umatilla, Tooele, and Pine Bluff. As of March 3, 2010, in Umatilla Chemical Depot (UCD), all of the GB and VX agent stored at the depot, 1531 tons of GB, HD, and VX stocks, had been incinerated, representing over 41% of the base's stockpile. In Anniston 69%, in Tooele 88%, and in Pine Bluff 71% of stockpiles have been destroyed.[103]

Early incineration technology usually subjected contaminated matter to a single burn. Upon evaluation of testing and operations at JACADS, the U.S. Army improved the technology further at the Tooele Chemical Agent Disposal facility (TOCDF). This "second-generation" baseline process consists of three stages: (a) separation of chemical agents, energetics (explosives and propellants), and related materials in preparation for incineration; (b) incineration of agents, energetics, and "dunnage" (packing and shipping materials) and the thermal decontamination of metal parts from munitions and storage containers; (c) treatment and monitoring of gaseous effluents and analysis and disposal of remaining solid and liquid wastes.[101] A brief overview of the agent destruction stage is provided here.

For the nerve agents, the incineration process is described by eq 1 for sarin and eq 2 for VX:

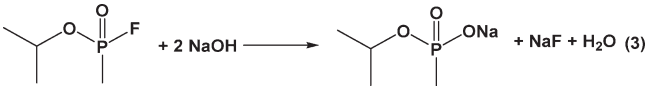




There are three furnaces in the system: the liquid incinerator (LIC), the deactivation furnace (DF) for energetics, and the metal parts furnace (MPF) to decontaminate the metal. The fourth incinerator, the dunnage incinerator (DUN), was intended but has not yet been put into operation. The liquid incinerator is a two-stage refractory-lined incinerator designed to destroy the nerve agents GA, GB, and VX (and mustard gases) and consists of two sequential combustion chambers and a pollution abatement system. Liquid chemical agent drained from the munitions or storage containers is collected in a storage tank from which it is fed into the first chamber, which is a high-temperature (1480 °C) liquid incinerator. This first chamber is preheated with natural gas. The fuel flow is controlled according to agent flow so as to maintain the appropriate temperature for effective agent destruction. Then, gases are sent to a second chamber, also preheated with fuel, for a final burn stage at a minimum temperature of 1090 °C (Scheme 6). The decontamination fluid is also used in the second chamber to ensure destruction of any residual agent. The afterburner gases are then treated in the pollution abatement system. During the operation of the system, some slag is produced in the second chamber. The fluids also contain salts, which are deposited in the bottom of the chamber. The slag removal system in TOCDF allows discharging molten salts during operations.[104]

3.4.2. Neutralization by Base Hydrolysis. While incineration is an attractive destruction approach, increasing public concern arising from the possible dangers from emissions of incineration facilities have led to the examination of alternative technologies for nerve agent destruction. Two alternative technologies for destroying nerve agent stockpiles were chosen by the U.S. Army: water hydrolysis followed by biotreatment and water hydrolysis followed by supercritical water oxidation.

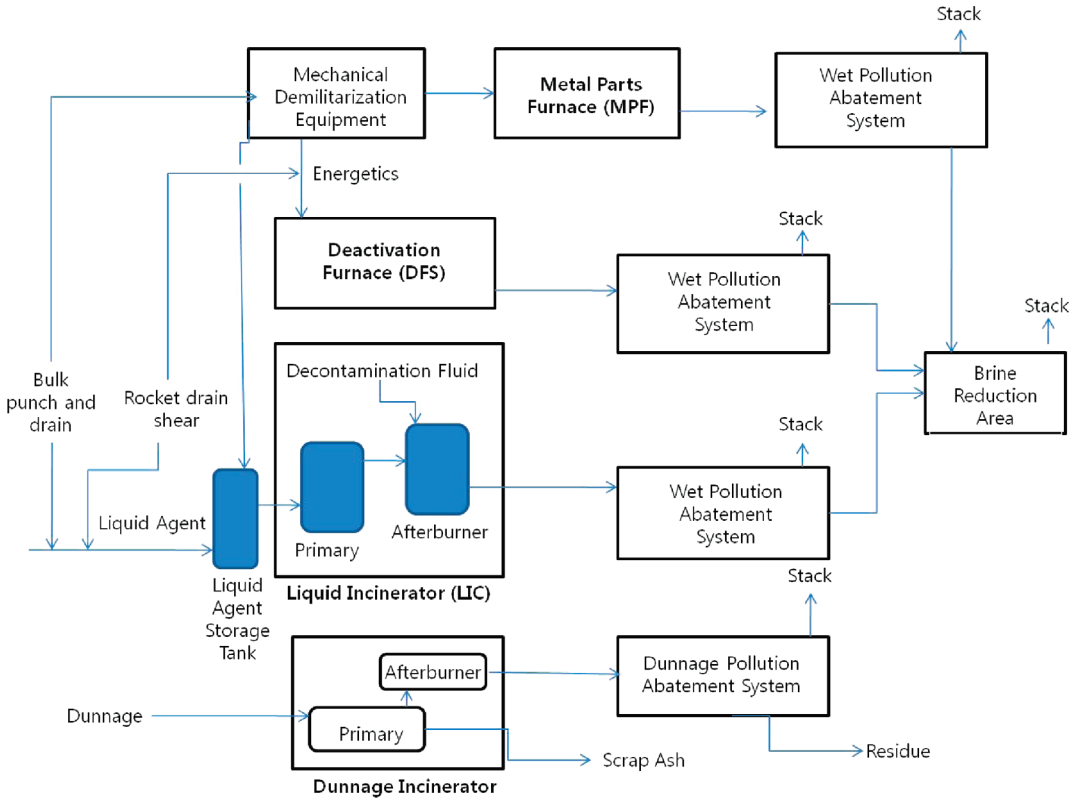
3.4.2.1. G Series. Neutralization with aqueous NaOH at ambient temperature allows for the destruction of significant quantities of sarin (GB). The hydrolysis of sarin has been studied extensively and is described by reaction 3. The technology was first used in the U.K., then in the U.S. and more recently in Iraq; 4188 tons of sarin were hydrolyzed successfully at the Rocky Mountain Arsenal (1973−1976).[102] Sarin is pumped into a holding tank. Then it is mixed with a large excess of aqueous sodium hydroxide to produce an aqueous solution of inorganic salts and the organic product of degradation. This material is packed into drums and deposited in a hazardous waste landfill. The water vapor before atmospheric discharge is subjected to a scrubbing process. Waste water is transferred to an industrial sump or lagoon.[105] In addition to those by the U.S. Army, neutralization processes have been used to destroy G agents in Great Britain, Canada, territories of the former Soviet Union, and Iraq.



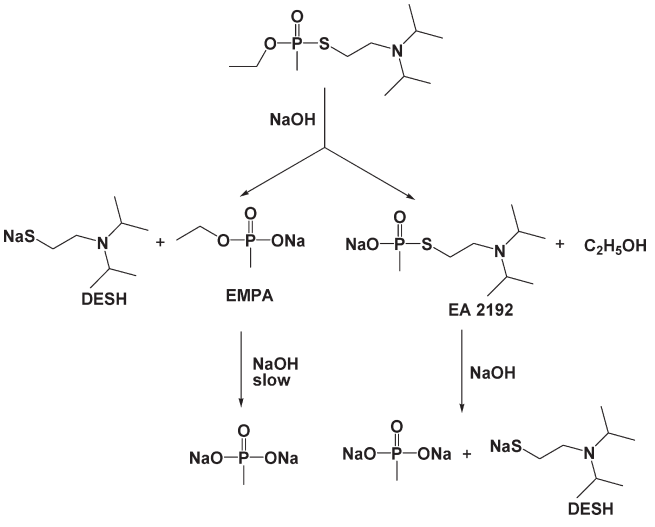
3.4.2.2. VX Agents. VX is also hydrolyzed[106] by sodium hydroxide (Scheme 7). At room temperature, nontoxic EMPA and toxic EA 2192 (but involatile and does not penetrate the skin) are stable, but they are hydrolyzed at elevated temperature to nontoxic products.[14] This methodology was used by the U.S. Army in neutralization processes at the Newport Chemical Depot. The agent from a holding tank was fed slowly into a vigorously stirred reactor containing aqueous sodium hydroxide solution preheated to 90 °C. Hydrolysis occurs at the organic−water interface, thus adequate reactor mixing is very important; VX is present as a separate organic phase. The total amount of VX added to the reactor is 21% of the hydrolysate (by weight) before addition of sodium hypochlorite. The mixture is heated for 6 h. After cooling, an equal amount of bleach solution (sodium hypochlorite) is added to oxidize reaction products. After bleaching, the amount of VX processed is equal to 10% of the final hydrolysate (by weight). The hydrolysate is analyzed periodically using gas chromatography/mass spectrometry. The concentrations of both VX and EA 2192 are found to be below 20 ppb.[100] The hydrolysate is subjected to further treatment and final disposal.

In 2003, neutralization followed by supercritical water oxidation (SCWO) was selected as the technology to destroy the chemical weapons stockpile at the Blue Grass Army Depot.[107] After neutralization and chemical analysis, the hydrolysate was transferred with oxidizing agent (air or oxygen) to the SCWO

Scheme 6. U.S. Baseline System Adapted from Ref 104



Scheme 7. Neutralization of VX with Sodium Hydroxide



section and heated to 600−650 °C under approximately 270 atm. The SCWO reaction mechanism generally follows free-radical chain pathways that involve important oxidative radicals, such as $^{\bullet}OH$ and $^{\bullet}OOH$. Within ∼30 s, the organic components are largely oxidized to water and sodium carbonate, phosphate, and sulfate, as well as gaseous nitrogen-containing products (e.g., N_2 and N_2O). After cooling with quench water, the mixture from the SCWO reactor is released through a pressure reduction system. The resulting effluent is a mixture of gases (O_2, N_2, CO_2), a concentrated aqueous salt solution, and entrained solid salts. The aqueous salts undergo distillation to remove water in the evaporating section. Salts crystallized from this solution are filtered and packaged for landfill disposal. The disadvantage of second-stage technology is the corrosion of heating and cooling elements on either side of the supercritical water reactor. Frequent replacement of the reactor liner was planned for the SCWO units at the Blue Grass Chemical Agent Destruction Plant. Several research papers focused on SCWO development have been published.[108−110]

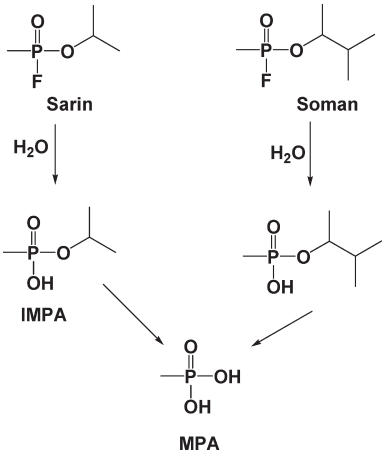
4. DECOMPOSITION REACTIONS

4.1. Hydrolysis

Since G-type nerve agents react with water, hydrolysis can be considered a basic method for detoxification.[111] Both soman and sarin are soluble in water and their hydrolysis under different pH conditions has been carefully studied.[112,113] Hydrolysis proceeds by phosphorus S_N2 nucleophilic attack (Scheme 8); the hydrolysis rate is temperature- and pH-dependent. This reaction gives the nontoxic products isopropyl methylphosphonic acid (IMPA) in the case of sarin and pinacolyl methylphosphonic acid in the case of soman. Hydrolysis of tabun gives phosphoric acid as a final product. Under neutral and basic conditions, hydrolysis occurs through the formation of *O*-ethyl-*N*,*N*-dimethylamidophosphoric acid and cyanide; under an acidic environment hydrolysis gives ethylphosphoryl cyanidate and dimethylamine (Scheme 9). Under neutral conditions, the rate constant is smaller than that of acidic and basic hydrolysis. At neutral pH and 25 °C, tabun is stable in water for 14−28 h; the half-life at

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

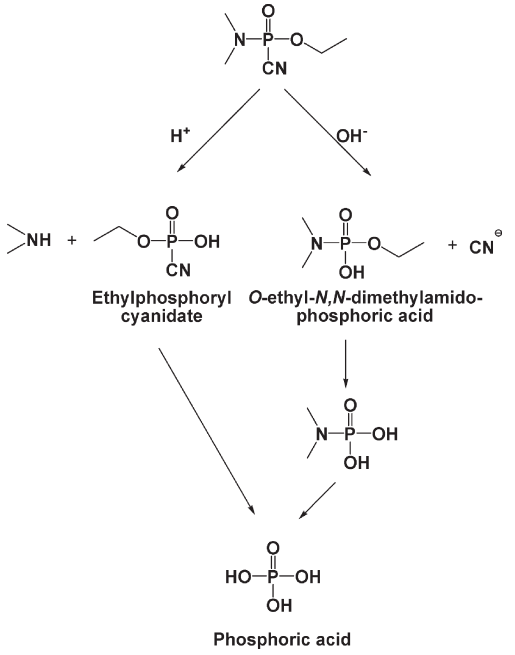
Scheme 8. Hydrolysis of Soman and Sarin to MPA



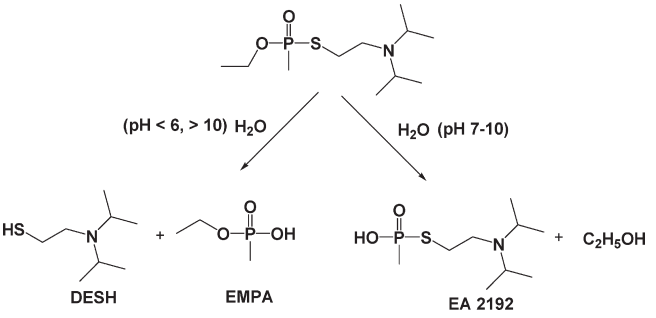
20 °C and pH 7.4 is approximately 8 h. At 20 °C and neutral pH range, the half-life of sarin is estimated from 461 h (pH 6.5) to 46 h (pH 7.5). At 25 °C, the half-life ranges from 237 h (pH 6.5) to 24 h (pH 7.5). A half-life of 8300 h at 0 °C and pH 6.5 indicates some persistence at low temperatures.[17] Soman is hydrolyzed five times slower than tabun; its estimated half-life is ~60 h at pH 6 and 25 °C. At pH greater than 10, both soman and sarin are hydrolyzed within a few minutes. Because an acid is produced, the pH decreases, and the rate of hydrolysis also decreased. Thus, excess base is required to maintain the same reaction rate.[2]

The hydrolysis of VX is complex and involves several pathways (Scheme 10). At neutral and weakly basic conditions, hydrolysis is slow with a half-life of 60 h. The rate constant decreases as pH decreases from 10 to 7.5. The reaction is catalyzed intramolecularly by the available amino group; either the *O*-ethyl or the *S*-alkyl group dissociates from the apical position, opposite the attacking H_2O molecule or the anionic phosphoryl oxygen (Figure 8).[14] At pH values of <6 and >10, cleavage of the P−S bond is the predominant process, resulting in the formation of ethyl methylphosphonic acid (EMPA) and diisopropylethyl mercaptoamine (DESH). In aqueous 0.1 M NaOH, a solution of 0.01 M VX was hydrolyzed to EMPA and *S*-(2-diisopropylaminoethyl) methylphosphonothioic acid (EA-2192) in a ratio of 87% to 13%, respectively; the reaction half-life here was 31 min.[17] This ratio is constant from 0.01 to 0.5 M NaOH, but decreases with increasing base concentration; in 4 M NaOH, it is 73% to 27%, respectively. Computational studies on the solvolysis of VX also indicate that the P−O and P−SR bond cleavage processes are kinetically competitive, but the P−SR cleavage pathway is favorable over P−OEt bond cleavage by 3.2 kcal/mol.[114,115] The same trend was observed for analogs of VX, DEMP and DEPPT. ^{31}P and ^{13}C NMR studies show that EA-2192 is produced from P−O, not O−C, bond cleavage.[14] EA-2192 is relatively stable in water; no degradation of EA-2192 was observed after 1000 h in distilled water.[17] EA-2192 can be hydrolyzed to DESH and MPA. However, at room temperature, the hydrolysis is exceptionally slow, and EA-2192 is considered to be approximately as toxic as VX. Therefore, unlike G agents, VX cannot be detoxified by *base-catalyzed* hydrolysis. But, basic hydrolysis at *elevated temperature* is used to effect neutralization. EA-2192 in concentrated NaOH at 90 °C gives the nontoxic species $MePO_3^-$ and thiolate (RS^-).

Scheme 9. Complete Hydrolysis of Tabun to Phosphoric Acid



Scheme 10. Hydrolysis of VX



Hydrolysis of R-VX is slower than VX under the same conditions and half-lives in unbuffered water at pH 7 are 12.4 days and 4.78 days for R-VX and VX, respectively. It was proposed that the bulky isobutyl group in R-VX inhibits the attack by water and subsequent hydrolysis more than the ethyl group in VX.[116]

4.2. Autocatalytic Hydrolysis or Hydrolysis Byproducts

VX and R-VX are completely hydrolyzed within 1−2 months at room temperature to nontoxic compounds **a** and **d** in the presence of a stoichiometric amount of water (Scheme 11).[117] The reaction is initiated by an attack of the deprotonated phosphonate (**b**) on protonated VX to produce the toxic diphosphonate (**c**). Diphosphonate is rapidly hydrolyzed to the acid (**a**), which is the carrier of the chain reaction. Since all reactions are reversible, except for the hydrolysis of the diphosphonate, a slight excess over the required equimolar water is recommended to ensure irreversibility; otherwise diphosphonate **c** will react 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**. The reaction proceeds only with organophosphorus

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

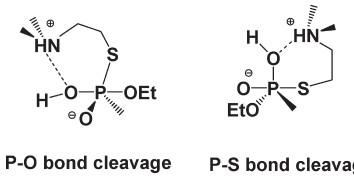
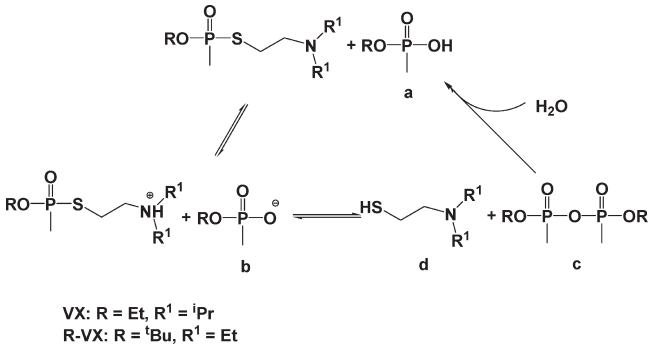


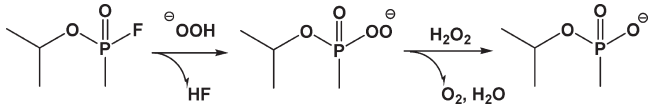
Figure 8. Intramolecular amino group-catalyzed hydrolysis of VX. Adapted from ref 14.

Scheme 11. Autocatalytic Hydrolysis Mechanism of VX and R-VX[a]



[a] Modified from ref 117.

Scheme 12. Perhydrolysis of Sarin[a]



[a] Adapted from ref 121.

esters with structures similar to the V-type agents (i.e., an intramolecular amino group is essential) and involves both intra- and intermolecular catalyzed reaction steps.

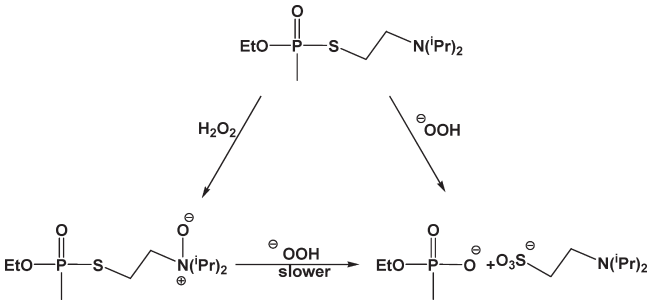
4.3. Use of Peroxide

Peroxides (R−O−O−R′) are attractive reactants for decontamination because they are nontoxic and noncorrosive.[118] Additionally, peroxides have low freezing points that make them suitable for the development of cold-weather decontamination solutions. Decontamination methods using the nucleophilic peroxy anion, HOO^-, have been known for decades.[119,120] The reaction proceeds through peroxyphosphonate intermediates, which can be supported by ^{31}P NMR analysis (Scheme 12).[121]

Density functional theory (DFT) has been used to show that the reaction of G agents with hydroperoxide is kinetically more favored compared with simple hydroxide.[122,123] Faster solvolysis can be explained by strong intermolecular hydrogen bonding in the transition state geometry.[123]

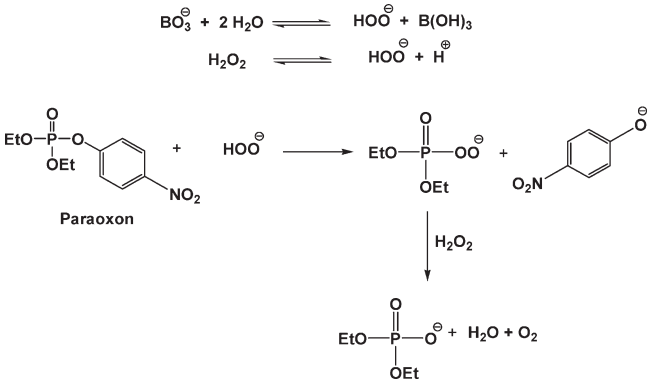
For G agents, perhydrolysis is fast, and they can be easily detoxified under dilute alkali conditions, whereas hydrolysis of V agents in basic solution is less effective. From this perspective, perhydrolysis of V agents (e.g., VX) is of more current interest. Another point here is that perhydrolysis avoids formation of toxic *S*-[2-(diisopropylamino)ethyl]-methyl phosphonothioic acid (EA-2192), whereas basic hydrolysis yields about 22% EA-2192. It was

Scheme 13. Perhydrolysis of VX[a]



[a] Adapted from ref 121.

Scheme 14. Dissociation of Perborate in Alkaline Aqueous Solution and Reaction of Paraoxon with Perhydroxyl Anion[a]



[a] Note: in kinetic studies other reactions such as alkaline hydrolysis of paraoxon and hydrolysis of boric acid, $B(OH)_3$, must also be considered. Adapted from M. D. David et al.[125]

shown that VX also undergoes rapid perhydrolysis to give phosphonic acid, but a peroxyphosphonate intermediate was not observed (Scheme 13).[14,121] The reaction is pH-dependent. Formation of acidic product stops the reaction before completion; thus, addition of bicarbonates as buffering components drives the reaction to completion.[14,121]

Perborate, mostly sodium perborate, $NaBO_3 \cdot nH_2O$, is an alternative detoxifying agent to hydrogen peroxide in terms of storage stability. In alkaline aqueous solution, perborate dissociates to borate $B(OH)_3$ and perhydroxyl anion (Scheme 14). The perhydroxyl anion (OOH^-) is more reactive than hydroxide toward organophosphates.[119,124] Several kinetic studies of perborate with organophosphates, including pesticides, were carried out.[125−127] It was established that the rates of decomposition of malathion, diazinon, parathion, methyl parathion, and mevinphos with sodium perborate at pH 10 are much higher than those in sodium carbonate, which was used as a control solution at the same value of pH. The half-lives of pesticides in perborate solution are estimated in minutes (e.g., ∼8.6 min for malathion in tap water (Davis, CA)), while in control solutions they are too long to be measured experimentally. Paraoxon also demonstrates 80-fold enhancement of decomposition rate in basic perborate solution compared with usual alkaline hydrolysis. This reaction rate depends on pH and concentration of perborate and slows down with increasing pH and borate concentration. The calculated rate constant for reaction with perborate is in good

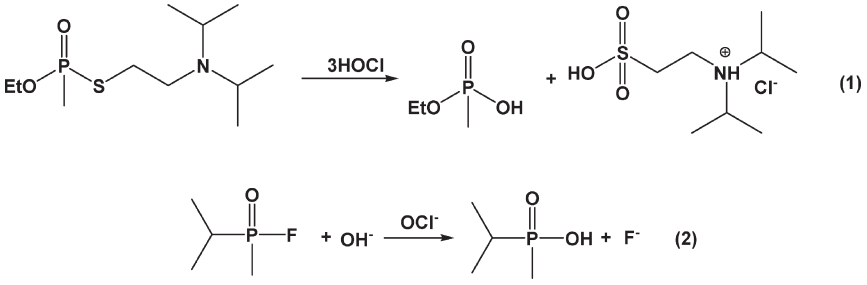
dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Table 1. Decontaminants Composed of Hypochlorites[a]

decontaminant	composition
bleach	aqueous solution of NaOCl (2−6 wt %)
HTH (high test hypochlorite)	$Ca(OCl)Cl + Ca(OCl)_2$ as solid powder or a 7% aqueous slurry
STM (super tropical bleach)	$Ca(OCl)_2 + CaO$ as solid powder or as 7%, 13%, 40%, or 70% aqueous slurries
Dutch powder	$Ca(OCl)_2 + MgO$
ASH (activated solution of hypochlorite)	0.5% $Ca(OCl)_2$ + 0.5% NaH_2PO_4 buffer solution + 0.05% detergent in water
SLASH (self-limiting activated solution of hypochlorite)	0.5% $Ca(OCl)_2$ + 1.0% sodium citrate + 0.2% citric acid + 0.05% detergent in water

[a] Adapted from ref 2.

Scheme 15. Reaction of VX with Hypochlorite (Reaction 1) and Hydrolysis of Sarin Catalyzed by Hypochlorite (Reaction 2)



agreement with literature data for perhydroxyl ion, confirming that perhydroxyl ion is the reactive species in this reaction.[126] High reactivity, commercial availability, and reasonably good storage stability make sodium perborate a viable option for destroying pesticide waste. However aqueous H_2O_2 is much more stable in storage than any solid peroxide compound.[128,129] For sodium perborate in particular, high humidities and temperatures above 90 °C must be avoided in storage, and it decomposes in warm or moist air.[130] Cool storage is required for this material. Aqueous H_2O_2 has less stringent storage requirements, and is it not as temperature sensitive with regards to decomposition.[131]

4.4. Oxidation with Bleach and Related Reagents

One of the most important categories of agent/pesticide decontamination reactions is oxidative chlorination. Solutions or solid bleach agents were the first form of chemical decontamination to be studied and were introduced during WWI. Bleach matrixes have also been tested with laboratory test animals.[132] First, bleach decontamination solutions are presented in Table 1.

Reactions of some nerve agents with bleach are represented in Scheme 15. Reaction 1 proceeds vigorously and rapidly via oxidative hydrolysis of the P−S bond. Under acidic conditions, only 3 equiv of active chlorine are required for each mole of VX. Importantly, VX is more soluble in acidic media because of tertiary amine nitrogen protonation; oxidation occurs at sulfur in the presence of HOCl. At high pH, the solubility of VX is reduced and oxidation at the amino moiety occurs accompanied by the evolution of chlorine or oxygen gas and formation of sulfate and carbonates. Under these conditions, over 20 mol of active chlorine is required per mole of agent.[2] In reaction 2, hypochlorite anion catalyzes the hydrolysis in aqueous solution at pH range of 5−9.[133]

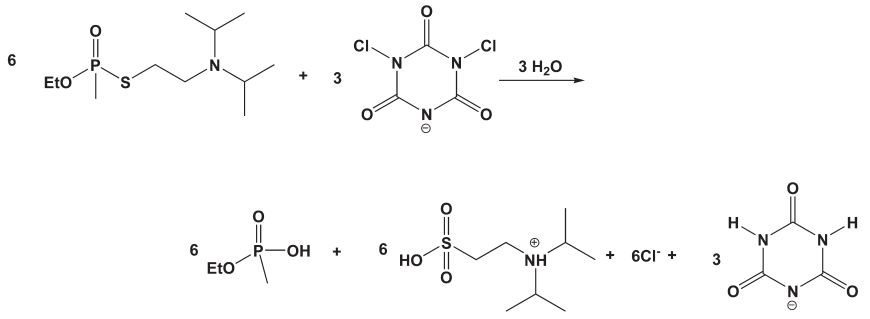
The micellar reaction kinetics of phosphorus esters catalyzed by hypochlorite was reported in 2002.[134] The usefulness of the hypochlorite−surfactant combination as a decontaminating agent was established through a kinetic study of the hydrolysis of three phosphorus esters and sarin in the presence of the CTABr/ClO^- system. In all cases studied at pH 8.5, the surfactant CTABr (cetyl trimethylammonium bromide) significantly enhanced the hydrolytic capability of hypochlorite. Sarin is completely decontaminated within 10 min at a sarin/hypochlorite ratio of 20:1 in a micellar CTABr−ClO^- mixture. In the absence of surfactant, it takes more than 70 min to detoxify sarin even at a 10 times higher concentration of hypochlorite.[133] There are some disadvantages in using bleach as a decontaminant: (i) the active chlorine content is reduced with storage time, so a fresh solution must be prepared prior to use; (ii) a large amount of bleach is required; (iii) bleach is corrosive to many surfaces. As a result, buffered solutions of bleach (Table 1) and more stable, less alkaline *N*-chloro compounds have been used. An aqueous solution of a commercial *N*-chloro oxidant, Fichlor (sodium *N*, *N*-dichloroisocyanurate) at pH 6 effectively detoxified VX but was not as effective for G agents.[2] HOCl is believed to be the reactive species (Scheme 16).

Other oxidants were developed and explored. Since G-type nerve agents can be easily hydrolyzed in basic media, oxidation is more realistic for V-type nerve agents. Oxidation of the sulfur in VX in aqueous acid medium is rapidly followed by hydrolysis to nontoxic products. One of the most effective oxidants is the commercial product DuPont Oxone, where the active ingredient is potassium peroxymonosulfate. An aqueous solution of Oxone has a pH of ~2, can dissolve a large amount of VX, and enables fast oxidation at the sulfur. In this case, only 3 equiv of oxidant are required per 1 equiv of agent (Scheme 17).[2] Based on Oxone, the L-Gel system was developed for decontamination of buildings and large scale materials. The system is relatively noncorrosive (pH ≈ 2.3).[135] Other peroxyacids such as magnesium monoperoxyphthalate (MMPP), peroxyacetic acid, and *m*-chloroperoxybenzoic acid (*m*-CPBA) in aqueous or aqueous−polar organic solvents detoxify VX.[14,136]

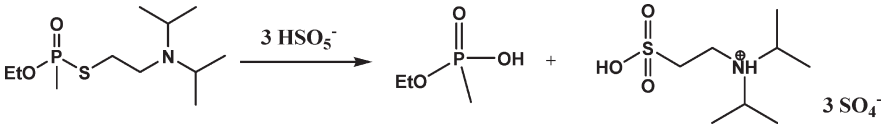
4.5. Alkoxide as Nucleophile

4.5.1. Basic Media. Alkoxide anion (RO^-) is a good nucleophile for the chemical destruction of organophosphonate

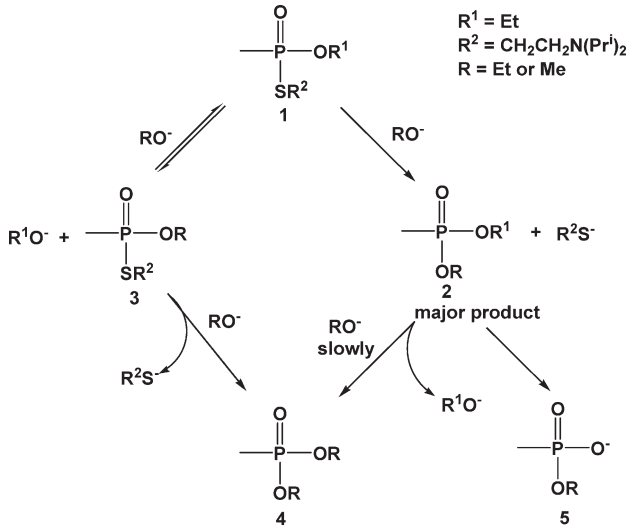
Scheme 16. Detoxification of VX with Fichlor



Scheme 17. Detoxification of VX with Oxone



Scheme 18. Reaction of VX with Alkoxide Anion[a]



[a] Adapted from ref 138.

nerve agents. Alkoxide solutions can be easily prepared mixing an alcohol with NaOH or KOH. Alkoxide reactivity increases with increasing size of the alkyl group (R). Cleavage of the P−S bond in V-type nerve agents such as VX is more effective than in simple basic hydrolysis and similar to perhydrolysis by peroxide. The reaction proceeds through displacement of thiolate by the alkoxide ion, but some loss of the *O*-alkyl group is also observed (e.g., **3** in Scheme 18). Both displacements occur with complete inversion of configuration at the phosphorus atom. The kinetic facial selectivity in displacement depends on intrinsic kinetic affinity of the alkylthio ligand to occupy either an axial position or an equatorial position in transition state.[137] VX reacts with 0.25 M CH_3O^- in methanol with a $t_{1/2}$ of 15 min at 22 °C.[14] The major product is the diester MeP═O(OR)(OR$_1$); but over time, this species reacts with alkoxide to give MeP═O(OR)$_2$ and alkyl methylphosphonate (**5**). For some compounds, the first-order rate constants have been calculated; for example, for the simulant DEPPT, a first-order reaction plot revealed $k = 7.08 \times 10^{-4}$ s^{-1}.[138] It should be noted that the reaction with alkoxide anion is also effective in nonaqueous media. When EOH (E = H, Na, K) is present in the reaction mixture, the hydroxide anion OH^- competes with RO^-, whereupon the toxic thioic acid species [MeP═O(SR^2)OH] is produced.

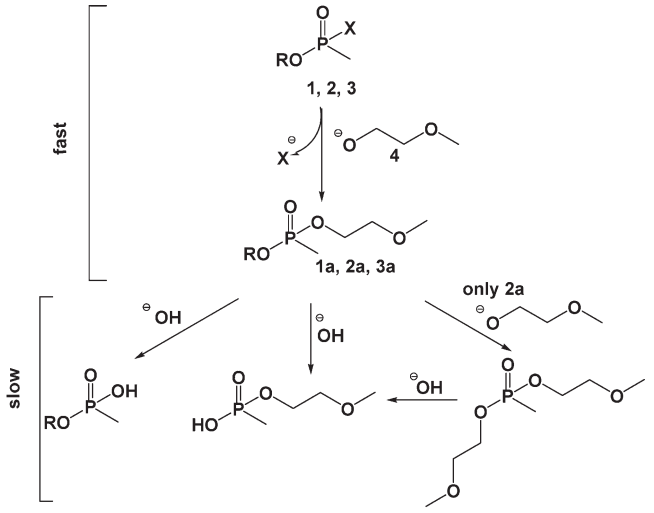
Other systems such as diols (e.g., ethylene diglycol), ether alcohols, or amino alcohols (monoethanolamine, MEA) are also used to generate alkoxide anions. Their reactivity increases as the solvent becomes less protic.[14] The standard decontamination solution, "DS2", contains the ether alcohol, ethylene glycol monomethylether, which gives **4** as a reactive species in Scheme 19. Compound **4** readily decomposes both G- and V-type nerve agents to give diesters as the major products. These diesters decompose further to give other products, but these reactions are slower. DS2 is a very effective decontaminant and is noncorrosive with long-term storage stability. It can be used in a broad temperature range (−26−52 °C) as well.[2]

4.5.2. Metal-Catalyzed Reactions. For organophosphonates, there are various metal-based approaches to hydrolysis revolving around the metal center and the ligand type. Also there are options regarding the number of metal ions involved. First, we will look at metal-catalyzed reactions. Then we will look at metal-assisted action as illustrated in detail below in Scheme 21. It should be mentioned that there are a wide variety of reports regarding solution catalytic cleavage of organophosphate P−O bonds by discrete metal/element complexes. The metal-catalyzed hydrolysis[1] literature is extensive, stemming from the ubiquity of phosphates in biology, that is, in the backbone of DNA/RNA, which may be cleaved hydrolytically through the use of metal complexes.

Metal-catalyzed hydrolysis of organophosphonate papers are by various principal authors such as Wagner-Jauregg and E. Bamann. Earlier papers deal with phosphate esters. In 1955, a report by Wagner-Jauregg et al. reported the hydrolysis of (^{i}PrO)$_2$P═O(F) via Cu^{2+} 2,2′-dipyridyl complexes;[139] this compound was found to be more effective than those whose ligands contain other nitrogenous bases. A poor performance

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Scheme 19. Reaction of VX, GB, and GD with decontamination Solution DS2[a]



[a] Adapted from ref 2.

with Cu^{2+}—EDTA confirmed that metal coordinative saturation shuts down catalysis. In the same year, a report by K.-B. Augustinsson et al. described metals used with phosphoryl-phosphatases.[140] Separately, A. E. Martell et al. studied the hydrolysis of sarin and DFP to determine that Cu^{2+} was an appropriate species for this process with a range of ligands.[112,141] The kinetics of hydrolysis of sarin catalyzed by cerous, cupric, and manganous ions was studied. Second-order rate constants were obtained, and these hydrometallic species with the formula $M(OH)(H_2O)_x^y$ are considered as catalytically more active than the hydroxyl ion.[142] There is also a cluster of early reports regarding the catalysis of phosphate esters by soluble metal ions by E. Bamann et al. (~1958—1962).[143—147] This work was performed in heterogeneous solvent systems specifically and posed difficulty for obtaining accurate values of rate constants. Then, there is an 1968 report of Mg^{2+}-enhanced hydrolysis of sarin.[148] In 1969, R. J. Withey studied the hydrolysis of $((p\text{-}NO_2)C_6H_4O)(OH)P{=}O(Me)$ with La^{3+} uncomplexed by an ancillary ligand. In this study, the rates were measured in aqueous media at near-neutral pH (7.3—9.0) at 70 °C; rate enhancements of 3.6×10^4 were found.[149] Also, a report by R. A. Kenley in 1984 details the hydrolysis of $[((p\text{-}NO_2)C_6H_4O)(OH)P{=}O(Me)]$ and $[((p\text{-}NO_2)C_6H_4O)(OEt)P{=}O(Me)]$ using Co^{3+} hosted by one tetra-nitrogen $[N_4]$ macrocylic system (1,4,7,10-tetra-azadecane-based) or two of the same bidentate systems (1,3-diaminopropane, 1,1,2,2-tetramethyl-1,2-diaminoethane, 2,2′-bipyridyl species).[150] The 1,1,2,2-tetramethyl-1,2-diaminoethane is the most active in promoting production of free $(p\text{-}NO_2)C_6H_4O$. The rate of hydrolysis (k_{app}) with 1,1,2,2-tetramethyl-1,2-diaminoethane—Co^{3+} was determined to be $15 \times 10^{-2}\ M^{-1}\ s^{-1}$ for $[((p\text{-}NO_2)C_6H_4O)(OH)P{=}O(Me)]$ and $5 \times 10^{-2}\ M^{-1}\ s^{-1}$ for $[((p\text{-}NO_2)C_6H_4O)(OEt)P{=}O(Me)]$.

Regarding more contemporary reports, studies concerning the generality of transition metal catalyzed hydrolysis were summarized by J. R. Ward et al. in 1990.[151] There was a report in 1985 of Co^{2+} hydrolysis of $(p\text{-}(NO_2)C_6H_4O)(OEt)P{=}O(Me)$ by

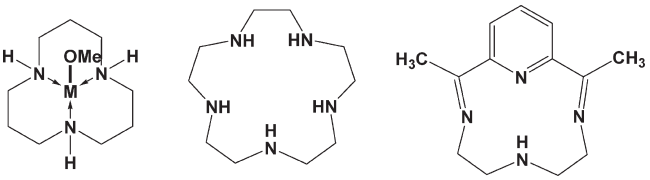


Figure 9. Ligands that have been used in exploring the hydrolysis of nerve agents and related species.

R. S. Brown et al.[152] A 1988 report represents a new strategy: P. R. Norman used a variety of metals in looking at monoaquo metal species.[153] Later, R. W. Hay et al., reported using $[Cu(tmen)(OH_2)(OH)]^+$ (tmen = *N,N,N′,N′*-tetramethylethylenediamine) with a variety of bases in the hydrolysis of 2,4-dinitrophenyl ethyl methylphosphonate.[154] F. Tafesse investigated hydrolysis of several nerve agent simulants by solution that contains $N_4Co(III)$ ion (N_4 = (ethylenediamine)$_2$, (trimethylenediamine)$_2$, or tris(3-aminopropyl)amine) in microemulsions.[155] Finally, a report by R. E. Lewis described La^{3+} catalysis with additional help from a (ligand)Zn—OCH_3 species.[156]

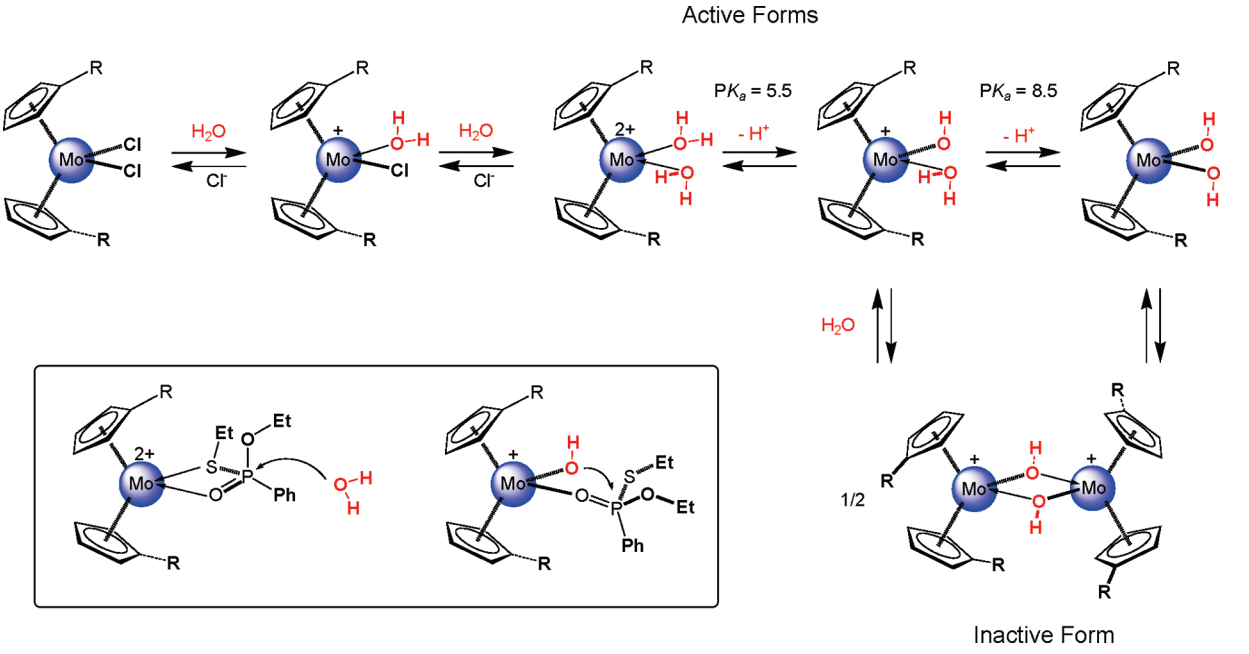
Similar catalysis was also adapted for materials and supports. R. W. Hay and co-workers reported a copper system that is capable of hydrolyzing sarin, 2,4-dinitrophenyl diethyl phosphate, and 2,4-dinitrophenylethylmethylphosphonate in metallomicelles. These transformations occurred at 35 °C and at a pH of 8. The hydrolysis enhancement for sarin was appreciable, and for 2,4-dinitrophenyl ethyl methylphosphonate enhancement was measured as 6.6×10^4.[157] E. L. Chang et al. reported methyl parathion hydrolysis using a polymer (trimethylolpropane trimethacrylate) and Cu^{2+} that was coordinated by a functionalized bipyridyl ligand.[158]

Metal-based hydrolysis studies have also included VX mimics. R. S. Brown communicated a Zn^{2+}-catalyzed series of phosphonothioates (EtO)(ArS)P═O(Me) (Ar = 3,5-dichlorophenyl, 4-chlorophenyl, 4-fluorophenyl, phenyl, 4-methoxyphenyl).[159] Also methanolytic cleavage of paraoxon promoted by solid supported lanthanide ion catalysts (La^{3+}, Sm^{3+}, Eu^{3+}, Yb^{3+}) was investigated.[160] Solid supports were chlorobenzylated silica and chloromethylated polystyrene, functionalized with two chelating agents (iminodiacetic acid and ethylenediamine-*N*, *N′*-diacetic acid). The catalysts showed good activity at pH values of 8.8 and 11 in methanol. Also, reusability of catalysts was discussed.[160]

A report by L. Y. Kuo shows that molybdenocene (Cp_2MoCl_2) can take part in *O,S*-diethyl phenylphosphonate hydrolysis; this study is elaborated below (Scheme 20).[161] Also, L. Y. Kuo and co-workers previously determined the cleavage of a thiophosphinate using a related organometallic system.[162,163]

The Kuo report represents a turning point for organometallic systems. The complex used is actually a well-studied compound type. Herein, the substrate underwent 100% cleavage of the P—S bond (pH 7.2, 30 °C). The [*ansa*-Cp_2MoCl_2] species and $[(CpMe)_2MoCl_2]$ were also studied. Scheme 20 provides a clear representation of the proposed active species. This report opens up possibilities for other metallocene systems; group 4 metal ions for instance have been exhaustively pursued in other applications. Scheme 20 clearly shows the attack on —OR and —SR in a well-defined system. In Figure 10, a short stack of ^{31}P NMR spectra shows the progression of the hydrolytic nucleophilic reaction by H_2O at phosphorus to give the P—OH substituent from P—OEt. One limitation with the L. Y. Kuo system is that it is not

Scheme 20. The Proposed Stepwise Catalytic Action of Molybdenocene on (EtO)(EtS)P═O(Ph)[a]



[a] Adapted from ref 161.

operational in pure water; an aqueous THF/acetone mixture was used due to the water insolubility of the phosphonothioate. Further, acetone was used to maintain one phase. However, there is currently some uncertainty of mechanism with this model system. Some of the aspects that plagued the early work cited above still could exist and do exist here: solvolytic dissociation of ligands and complication of mechanism by multimers, that is, formation of dimers.

4.5.3. Metal-Assisted Reactions. Noncatalytic, nonsurface particle systems have also been reported to facilitate NA degradation and likely detoxification. One main type of reaction involves PO−R bond cleavages. D. A. Atwood et al., have reported several examples in which the alkyl fragment is lost from the organophosphonate leading to a bound phosphonate element−phosphate ester.[12,164] Group 13 element-mediated sensing and degradation was possible using either an aluminum or boron reagent (Figure 11).[165] In the reaction, the NA coordinates to the cationic group 13 element activating the phosphate ester group for nucleophilic attack by the bromide anion. Separately, in 1997, a lanthanum hexaaza-crown species was studied.[166] There is also a report by D. R. Leslie in which ozone was used in conjunction with Co^{2+}, Cr^{3+}, and Mn^{2+}; this older report involved a G-type agent.[167] There are other examples of metal assistance for pesticides such as paraoxon.[168]

4.5.3.1. General Comments. The various systems described above dealt with two general types of chemical systems. The obvious question is whether a single or double or perhaps multiple site system is better for catalysis. There is much support generally for the bimetallic site. The prevalence of systems in which the site adjacent to agent binding allows for the activation of water for incipient nucleophilic attack is a theme that is also discussed with surfaces and enzymes (See Scheme 21).

4.5.4. Biotechnological Degradation. Perhaps the most intriguing aspects of organophosphonate nerve agent sensing and decontamination are the biological ones,[22,23,25,26,169,170]

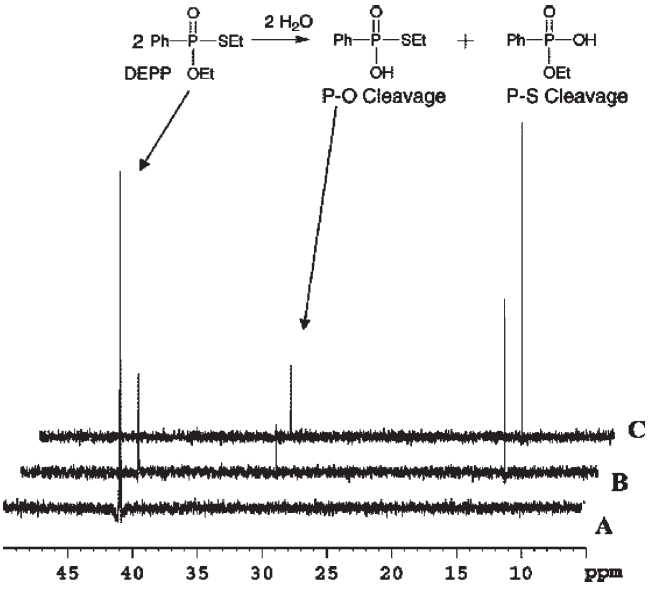


Figure 10. The ^{31}P NMR spectrum of DEPP, 25 °C, 0.1 M NaOH: (A) $t = 0$; (B) intermediate; (C) completion of reaction. Copied directly from ref 161. Licensee: David G. Churchill, Lincense Number: 2582911374387, License Date: Jan 06, 2011.

because there are many molecular aspects we do not understand. There is an enormous amount of literature on phosphate cleavage by discrete and carefully characterized metal complexes especially including those of Zn^{2+}, Fe^{2+}, and combinations of these two metals. This literature has been the subject of many reviews, including some recent reviews.[171−175] Nearer to our purposes here, important enzymes have been studied in both agent degradation and sensing. These important enzymes (*vide infra*), while sometimes mutated, can come ultimately from

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

organisms. Thus, this literature, which stretches back beyond the 1970s, is not immediately accessible for chemists because there are reports based on particular microorganisms or stewy mixtures of microorganisms that have or have not been completely characterized. However, the results are indeed of chemical relevance; depending on the enzyme, selective P−F or P−C cleavage may be achieved.

4.5.4.1. Whole Organism and Cell Studies. 4.5.4.1.1. Human, Animal, and Bacterial Studies. A founding paper in the emergence of nerve agent biotechnology is the A. Mazur et al. report from 1946, which revealed that $(^{i}PrO)_2P{=}O(F)$ was degraded in humans, rabbit, and monkey by a then-unspecified enzyme.[176] Plasma and tissue samples were studied. Importantly, the P−F bond was cleaved *selectively* giving $(^{i}PrO)_2P{=}O(OH)$; and the analysis of fluoride ion (F^-) was quantitative (there was no evidence of $(HO)_2P{=}O(OH)$ formation). Other fluorophosphates were investigated as well, such as $(MeO)_2P{=}O(F)$, $(EtO)_2P{=}O(F)$, and $(EtO)(MeO)P{=}O(F)$. Absolute enzyme inhibition was possible with high Hg^{2+} concentration, whereas partial (~50%) inhibition was effected upon treatment with Cu^{2+} or I^-; effects of other additives were less pronounced. Interestingly, at *low* Hg^{2+} concentration, the rate was enhanced. Various organs were studied, and the liver was determined to be the target organ of greatest inhibition.

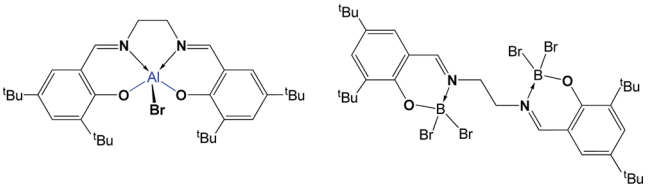
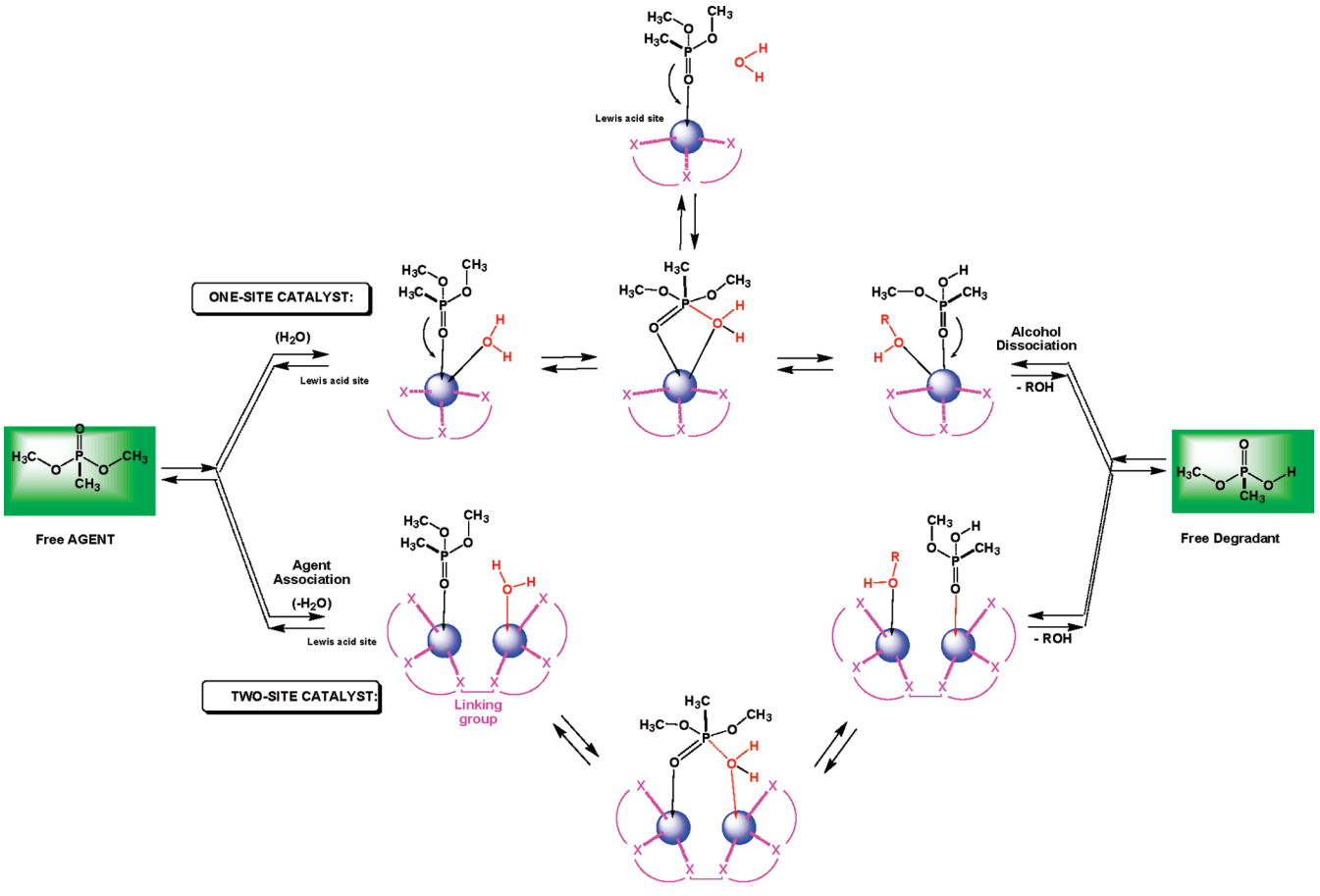


Figure 11. Structures of various group 13 chelate compounds that have been used in the dealkylation of nerve agents and related species.

In the mid-1950s, K.-B. Augustinsson published several papers related to an enzyme, called "tabunase", found in the blood plasma of several animals and in human blood plasma that hydrolyzed tabun.[177−183] Analysis of reaction products was carried out;[181] and properties of "tabunase" including its effect on the inactivation of cholinesterases by organophosphorus compounds were studied.[180,183]

It is important to acknowledge that the utility of discrete bacteria may facilitate OP degradation. There are general reports of bacteria published within the last ~35 years that should also be mentioned. A cluster of reports by D. M. Munnecke and coworkers was published in the 1970s. Herein, generally parathion was used in relatively high concentration to elucidate degradative pathways. The first paper in 1974 reports the decontamination of parathion and the formation of *p*-nitrophenol as a hydrolysis product.[184] A mixture of "microbial culture" was used to treat parathion; degradation was observed at a rate of 50 mg of analyte/(L·h). Herein, some microorganisms were tentatively identified. Next, parathion was studied in xylene (95% xylene solution (*o*-/*m*-/*p*-xylene mixture)) of relevance commerically, since xylene is a parathion carrier.[185] A subsequent report tries to tie together the metabolic paths that these enzymes take in

Scheme 21. Proposed Hydrolysis or Nucleophilic Attack (Methanolysis) for a One- and Two-Site Metal- or Element-Based Catalyst



dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

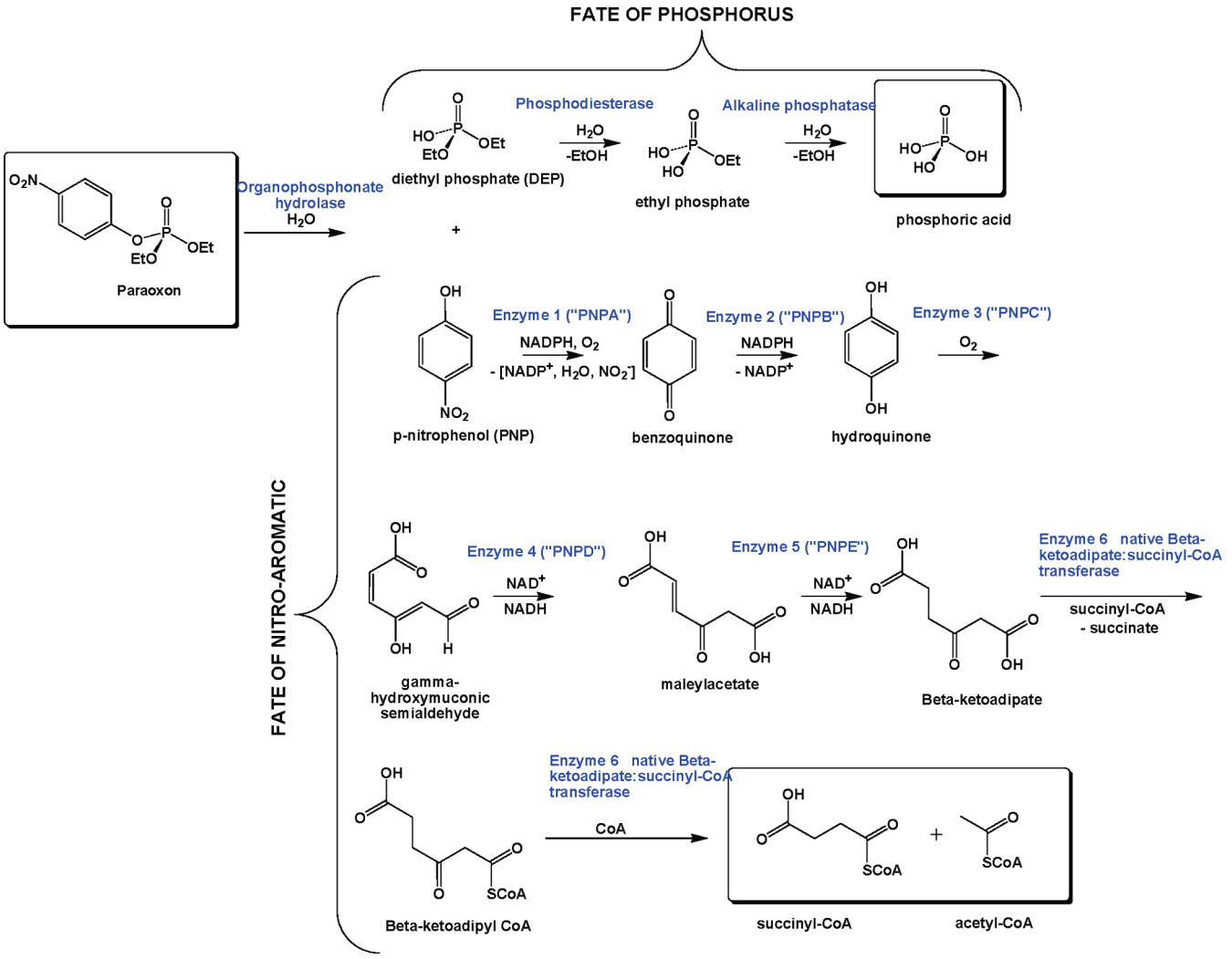
degrading the agents.[186] In this report, hydrolyis routes were identified; one gave (i) a principal degradative route to diethylthiophosphoric acid and *p*-nitrophenol. Two other degradative pathways were also uncovered: (ii) a route that leads to oxidation of parathion to paraoxon, followed by nitrophenol dissociation, thus leaving diethylphosphoric acid; (iii) a third route involved the amination of the parathion phenoxyl group. This derivative can then be hydrolyzed to *p*-aminophenol and diethyl thiophosphoric acid. In a report by D. M. Munnecke,[187] eight pesticides studied were found to be hydrolyzed; here a crude cell extract was used, not the whole cell. Parathion was hydrolyzed at a rate of 416 nmol/(min·mg protein); pH dependence in degradation was studied (optimum conditions, pH 8.5−9.5, 35 °C). Then, in 1977 there was a study of these enzymes immobilized on glass.[188] Next, there are a couple of reports by A. M. Cook et al. dealing with how the degradation products of pesticides [$(RO)_2P{=}O(OH)$, $(RO)_2P{=}S(OK)$, $(RO)_2P{=}S(SK)$, $(Ph)P{=}O(OH)_2$, $(RO)PhP{=}O(OH)$, $(RO)PhP{=}S(OK)$, $CH_3P{=}O(OH)_2$, and $(RO)RP{=}O(OH)$] are broken down by bacteria. Ionic versions of $(RO)_2P{=}S(OK)$ and $(RO)_2P{=}S(SK)$ were reported; these compounds were extensively and variously degraded.[189] In a subsequent report, A. M. Cook et al. categorize the various phosphonates that could be used as a phosphorus source. The examples include various derivatives including amino-containing derivatives. In particular, 2-aminoethylphosphonic acid could be used as a C, N, and P source for bacteria.[190] Next, *Pseudomonas putida* used $((NH_2)CH_2CH_2)P{=}O(OH)_2$ as a sole carbon source, an unprecedented demonstration. Here, it was noted that the addition of one phosphate could alter the consumption of another phosphate, etc. Studies with low analyte concentration were also performed. Phosphite acted as an inhibitor, however. In two previous papers, C−P scission with 2-phosphonoacetaldehyde phosphohydrolase was identified through studies by La Nauze and co-workers.[191] Next, L. P. Wackett et al. reported C−P scission with *Agrobacterium radiobacter* bacteria.[192] Bacterial strains were characterized based on how they acted on phosphonic acid. Herein, degradants and reaction rates were revealed for derivatives such as $R{-}PO_3^{2-}$, in which R included $^{+}H_3NCH_2CH_2{-}$, $H_3C{-}$ and Ph−. The best growth rate was found for $HOPO_3^{2-}$ itself. DFP was also analyzed by H. Attaway in 1987.[193]

4.5.4.1.2. Escherichia coli. Various reports center on the use of *E. coli*. In the M. L. Cordeiro et al. report of 1986, a homologous set of OPs were analyzed $(CH_3(CH_2)_n{-}P{=}O(OH)_2$ [n = 0−5].[194] This reaction gave pure hydrocarbon products: specifically, the respective 1-alkenes were detected in the headspace. Here, radical-based chemistry was invoked as the probable mechanism; the production of alkenes requires a skeletal rearrangement and would involve a cyclopropylcarbinyl radical. Thus, $Hg(OAc)_4$ was used as a reagent to help elucidate this proposed mechanistic pathway. L. Z. Avila et al. studied $(NH_2CH_2)P(=O)(OH)_2$ and related species; a mutant of *E. coli* was prepared that did not possess its native ability to decompose aminomethyl phosphonates.[195] This suggested that alkyl- and amino-methyl-phosphonates share the same mechanistic pathway of biodegradation. $^{13}C/^{14}C$ labeling aided this analysis. Three possible pathways were proposed but are not directly applicable to nerve agents because of the different amino position, in contrast to that for VX. In 1991, L. Z. Avila et al. reported a study of ethylphosphonic acid systems as well, which involved an incorporation study of ^{32}P.[196] In 2003, E. S. Gilbert et al. studied engineered *E. coli* SD2, along with *P. putida*, for the degradation of parathion.[197] Herein, samples containing 500 μM parathion were hydrolyzed. Furthermore, *p*-nitrophenol was also degraded (mineralized). These two bacteria were studied as a biofilm as well. A. A. Wang et al. focused on genetically engineered *E. coli* in which the cellulose binding domain and OPH were expressed together on the cell surface.[198] These cells were studied in CELLMAX artificial capillary cartridges (Celulosic Co., no. 400-022) in which paraoxon degradation were monitored (0−60 min). Herein, a buffer solution was used; $CoCl_2$ was also added for the maintenance of OPH activity. S. Y. McLoughlin and co-workers reported an *E. coli* that coexpressed two phosphotriesterases.[199] This paper emphasizes genetic considerations (amino acid sequences) and provides limited chemical detail regarding the chemical fate of paraoxon whose degradation was studied.

4.5.4.1.3. Pseudomonas (putida)-type Bacterial Degradation Reports. Systems involving bacteria of the genus *Pseudomonas* have also been studied. First, from a report by C. G. Daughton and co-workers in 1979, *P. testosteroni* was able to fully degrade *O*-alkyl alkylphosphonate via C−P cleavage.[200] Other bonds (e.g., P−OR) were also hydrolyzed during this molecular degradation. The ionic versions of the following organophosphates were studied: $CH_3P{=}O(OH)_2$, $[(CH_3)_2CHO]CH_3P{=}O(OH)$, $[(CH_3)_3CCH(CH_3)O]CH_3P{=}O(OH)$, $CH_3CH_2P{=}O(OH)_2$, $(CH_3CH_2O)(CH_3CH_2)P{=}O(OH)$, $(CH_3CH_2O)(CH_3CH_2)P{=}S(OH)$, $CH_3CH_2CH_2P{=}O(OH)_2$, $(CH_3CH_2O)(CH_3CH_2CH_2)P{=}O(OH)$, and $(NH_2CH_2CH_2)P{=}O(OH)_2$. Interestingly, in this study, RHgCl was found to serve as an inhibitor with the R−Hg bond being resistant to cleavage. A. M. Cook et al. studied the desulfurization of the species $(EtO)_2P{=}S(O^-)$ and $(EtO)_2P{=}S(S^-)$ through treatment with *P. acidovorans* (orthophosphate buffer).[201] The sulfur was consumed by the bacteria, but the mechanism could not be clearly inferred. A report by C. M. Serdar and co-workers details a *P. diminuta* parathion hydrolysis.[202] P−OAr bond hydrolysis was maintained as well as bacterial growth. A report by E. Zboinska et al. considered 25 different organophosphonates as sole carbon and nitrogen sources for *P. fluorescens*.[203] Bacterial growth was successful only for (*D*,*L*)-4-$NH_2(C_6H_5)CHP{=}O(OH)_2$, 2-aminoethyl phosphonate $[NH_2CH_2CH_2P{=}O(OH)_2]$, aminomethylphosphonate $[NH_2CH_2P{=}O(OH)_2]$, diisopropyl-9-amino-fluoren-9-ylphosphonate [9-(9-NH_2)(fluorenyl)$P{=}O(O^iPr)_2$], and 2-oxoalkylphosphonates $[R(C{=}O)CH_2P{=}O(OH)_2]$ as phosphorus sources. The species $NH_2CH_2P{=}O(OH)_2$ was a metabolite of glyphosate [*N*-phosphonomethylglycine]. A report by A. W. Walker et al. from 2002 involves an engineered *P. putida* and will be described below in Scheme 22.[204] Next, Y. Lei in 2005 reported the use of a *P. putida*, which featured a cellular surface organophosphorus hydrolysis.[205] The organophosphonate and the nitroaromatic groups of the substrate underwent decomposition. The extent of hydrolysis for paraoxon (7.9), parathion (3.5), and methyl parathion (1.5) in these systems was measured (in units of μmol/(h·mg dry weight)). M. Kulkarni and co-workers in 2006 reported the biodegradation of *p*-nitrophenol by *P. putida*.[206] This report is significant because of the prevalence of *p*-nitrophenolic substituents in pesticides. That *P. putida* can enable the decomposition of *p*-nitrophenol as well as phosphonates is notable. In 2006, de la Peña Mattozzi et al. reported a rationally designed pathway in *P. putida* (*vide infra*).[207]

The *Pseudomonas putida* report by de la Peña Mattozzi, which involves a muticomponent system, is intriguing because the end

Scheme 22. Complete Engineered Enzymatic Degradation of Paraoxon[a]



[a] Adapted partly from ref 207.

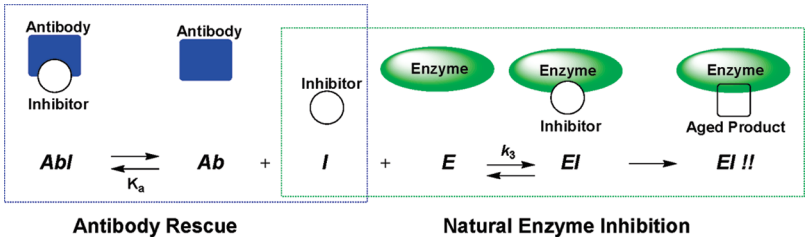
result gives mineralized products.[207] The steps are all described in Scheme 22. This report is related to the research group's previous study of parathion degradation into chemical (carbon) and other components.[197,204] The fate of the nitrophenol is of relevance in biodegradation and has been seen in a previous report by this group and others.

4.5.4.2. Isolated Enzymes. Once a clear understanding of protein structure has been made, stepwise modifications of agent degrading proteins, for example, OPH, can be undertaken. Such tailor-made systems may lead to effective catalysis; adaption for use in sensing arrays can then be made. First, when a metalloenzyme is considered, the simplest change is metal ion substitution. However, when the metals are changed for an apoenzyme sequence, different folding may ensue; upon remetalation, denaturation could occur. After all, different folding may give a different active site. In any event, steric and kinetic differences may be evident. Next, the peptide sequence can also be altered. By substitution of one residue (or single or multiple amino acid segments), functional differences in agent hydrolysis can also be achieved. Herein, organophosphonate cleavage is thought to occur in approximately the same way as the cleavage of phosphates. The proposed discrete steps in catalysis for one- and two-centered species were shown above in Scheme 21.

4.5.4.2.1. Nature's Catalysts: Organophosphate-Cleaving Enzymes. Organophosphate hydrolase (OPH) is an enzymatic protein composed of two lobes. It is usually obtained from *Pseudomonas diminuta*. In the native state, each lobe bears a dizinc site. The catalytic performance is relatively much better against parathion and paraoxon and much worse for VX. There are various select enzymes whose natural role may not be established but which can measurably degrade nerve agents and pesticides. Two types of these are organophosphorus acid anhydrase (OPAA) and organophosphorus hydrolase (OPH). The sequences and structures of both OPAA and OPH are known. Some major contributors include the research groups of J. J. DeFrank (U.S. Army Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, Maryland). One report by DeFrank et al. involves the substrate $(^{i}PrO)_2P{=}O(F)$, which was used (pH 8.5, 50 °C) with "OPAA 2" (~60 000 kDa).[208] The ions Mn^{2+} and Co^{2+} were used to stimulate the enzyme.[208] An ion-specific electrode could monitor F^- formation. Next, the report by S. P. Harvey et al. deals with the hydrolysis of

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Scheme 23. Antibody Rescue and Enzyme Inhibition[a]



[a] Adapted partly from A. A. Brimfeld et al.[217]

cyclosarin.[209] Two enzymes were measured from *Alteromonas* sp. JD6.5 (aka, "OPAA-2") and *A. haloplanktis*.[209] In 1996, T.-C. Cheng et al. reported an OPA anhydrolase. It was also studied with $(^{i}PrO)_2P(O)F$; OPAA-2 activity was also studied.[210] A report on organophosphorus hydrolase by C. M.-H. Cho et al. in 2002 deals with cell surface studies like the A. A. Wang et al. report above.[211] Here, a truncated form of the ice nucleation protein was used to isolate OPH variants with parathion degradative ability. Mutations in the active site of OPH, for example, H254R, H257L and H254R/H257L, affect catalytic characteristics, improving them for larger substrates due to enhancing structural flexibility.[212]

4.5.4.2.2. OPH Conjugates with Synthetic Materials. There are noteworthy OPH conjugations and immobilizations that allow for hydrolysis (degradation) in convenient ways. First, there was a report involving firefighting foams that contained a portion of organophosphorus hydrolase (E.C. 3.1.8.1) found to be effective in extracting and neutralizing NAs.[213] Enzymatic activity was said to be retained at the liquid/air interface. Next, there is a report involving "nanocomposite protein−silicone polymers" prepared in a variety of forms; these were found to be effective in decomposing tested analytes involving paraoxon, dichlorvos, and $(^{i}PrO)_2P{=}O(F)$ in gas or liquid form.[214] Finally, a report by A. H. Mansee et al. involved OPH conjugations to cellulose, which can be prepared on a column or stirred.[215] Herein, paraoxon and coumaphos were tested; degradation was found to occur in the "column", but stirring was found to be more effective. In these accounts, it was meant for the degradation to occur at the *enzyme active site*, and conjugation can be performed in a variety of ways. However, interaction of the agents with the conjugated material or support needs to be eliminated as a possibility by performing the necessary control experiments.

4.5.4.3. Antibodies/Immunology-Related Strategies. The exploration of antibodies in nerve agent sequestration and decontamination has also arisen out of the biotechnological approach. A review in 2007 by Lenz et al. underscores many of the previous strategies and recent trends, as well as the utility of poly(ethylene glycol)-coated r-HuBuChE.[216] Herein, there exists the ability for sequestration but not necessarily destruction; hydrolysis might occur but may not. Scheme 23 summarizes the general approach and workings of enzyme and antibodies in the context of this review. The cartoon illustrates the equations that produce constants, for example, K_a and k_3. The actions of antibody and enzyme inhibitors are both shown in which there may be a mutual inhibitor for both. A 1985 report by A. A. Brimfeld et al. involves mouse monoclonal antibodies that were shown to have stereochemical preferences for soman.[217] In this report, both antibodies share the same preference in binding for the two P(−) centered of four total species. Soman can be stereospecifically modified via enzymatic activity.[218,219] The [P═S] derivatives of soman and methylphosphonic acid were not preferred. A lowered number of methyl groups on the pinacolyl side chain reduced agent−antibody affinity. This P═*O*/P═*S* difference was also found for paraoxon/parathion in a separate study invoking an analysis of hydrogen bonding.[220] For instance, the systems $(EtO)_3P{=}O$ and $(EtO)_3P{=}S$ were studied in the 1960s with respect to their intermolecular hydrogen bonding capacity (with, e.g., phenol). The K_{as} values were reported as 330.5 and 4.5 (20 °C, solvent CCl_4); also the ΔH values (kcal/mol) were −6.7 and −3.2. The P═S frequency differences ($\Delta(\upsilon)$) were 30 cm^{-1} (solvent CCl_4), and 16 cm^{-1} (solvent CS_2).

In a separate report in 1986 by Ngeh-Ngwainbi et al., parathion antibodies were placed on a piezoelectric crystal.[221] This study involved gas-phase agent ineractions that were reversible, not degradative. The A. C. Buenafe et al. report in 1987 used eight monoclonal antibodies whose site specificities for soman were compared; herein, a mouse (murine) model was used.[222] The action of these monoclonal antibodies could be compared with that of phosphocholine-specific ones [phosphocholine = $(Me_3N^{+}CH_2CH_2O)P{=}O(OH)_2$]. A 1989 report by M. H. Erhard et al. involved an enzyme-linked immunosorbent assay (ELISA) model that involved MATP [$(p\text{-}NH_2C_6H_4O)P{=}O(CH_3)(OCH(CH_3)C(CH_3)_3)$].[223] Monoclonal antibodies involving mouse immunization and MATP were covalently attached to HSA; no interactions with tabun and VX were observed, and minimal ones were found with sarin. Also, there is a report by M. H. Erhard for soman detection.[224] A 1992 report by D. E Lenz focused on hybridomas that express antisoman antibodies.[225] IC_{50} values for soman were determined here: 1×10^{-4} to 5×10^{-6}. These antibodies were not "cross-reactive" with sarin, tabun, and pinacolylmethyl phosphonic acid (hydroxyl soman) [$((CH_3)_3C(CH_3)CH)P{=}O(OH)_2$]. A report by M. Glikson et al. from 1992 involved a different approach for soman: a remote site attachment at the pinacolyl end ($-CH_2COOH$ in place of −H). Also, a hydride (P−H) was used in place of the fluoride ligand (P−F).[226] The protein BSA and keyhole limpet hemocyanin were utilized. This paper addressed differently the need for high affinity, and a covalent succinamido attachment was used. Soman can age quickly when bound to AChE, making it hard to remediate the enzyme and creating a challenge for reactivation. A sulfur-based mimic was employed here: $CH_3S{=}O(OCHMeCMe_3)$. An M. H. Erhard et al. report from 1993 tackles soman detection systems.[227]

Next, antibodies for VX were explored by J.-M. Grognet in 1993.[228] Here, antibodies were functional *in vitro* only. Ten VX "haptens" were covalently bound to BSA or KLH. While the

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

produced and characterized antibodies can neutralize VX inhibition of AChE, soman and sarin affinity were reported as well. In 1995, Y. Ashani et al. studied the regeneration possibilities of phosphorylated mouse AChE conjugates using various oximes.[229] Important points such as nucleophilic strength, orientation, and the nonaged portion of the enzyme were considered in early studies[230,231] and in a related paper by L. Wong et al.[232] Mutants of mouse AChE (rMoAChE) were studied to elucidate which AA's influenced this important reactivation. Importantly, this regeneration is related to agent decontamination pathways because of the hypothesized limited toxicity of the phosphoryl−oxime adduct formation; this conjugation naturally allows for a restored AChE enzyme and phosphonate degradant byproduct. A report in 1999, by J. Yli-Kauhaluoma et al. involved a (pentacoordinate) organophosphorane species [MeP(O$(CH_2)_5$-NH_2)(OCHMeCMe$_3$)*O*,*O*(bridging-C_6H_2(2,4-di-Bu^t))];[233] this species resembles soman expressed as its transition state structure.[234] The hydrolysis was also studied theoretically. Next, a P. Vayron et al. 2000 report studied antibodies with Ph(EtO)P═O$(SCH_2CH_2N(^iPr)_2)$,[235] which was used as a simulant for VX. An α,α-difluorophosphinate hapten was synthesized in which the hydrolysis was effected at pH 7.4 (25 °C). In this study, the catalytic increase was 14 400 M^{-1}, over that for uncatalyzed hydrolysis. A paper by Z. Kovarik (2004) involved certain mutants of mouse AChE (EC 3.1.1.7) in which the choline binding pocket (Y337A, Y337A/F338A) and the acyl pocket (F295L/Y337A, F297i/Y337A, F295L/F297i/Y337A) were varied to gain an understanding of structure−function relationships.[236] These mutants were treated with [(RO)P═O(Me)$SCH_2CH_2NMe_3^+$)][$CH_3SO_3^-$] (R = cycloheptyl, isopropyl, dimethylbutyl) to effect phosphorylation; both R_P and S_P enantiomers were studied. The poisoned enzymes were able to be reactivated through the use of oximes (HI-6 and 2-PAM). The mutants could be compared in detail with the wild-type enzyme, which, interestingly, was outperformed by the Y337A mutant. Readers might be directed here to a report by B. P. Doctor et al. who prepared a thorough perspective of bioscavengers for human protection in 2005.[237] J. K. Johnson et al. in 2005 reported three soman-specific monoclonal antibody systems involving species that are protein-bound: [$((CH_3)_3)$-C(CH_3)CH)P═O(Me)$(OC_6H_4N$═N—protein)] and [(protein—$CH_2(CH_3)_2$)C(CH_3)CH)P═O(Me)(OCH_3)].[238] A recent report by Z. Kovarik (2007) details the mutations of AChE that can serve as catalysts for the cycloheptoxide compound [(C_7H_{13})P═O$(SCH_2CH_2$-$NMe_3)$(Me)] [$CH_3SO_3^-$].[239] Mutations such as F295L/Y337A, Y337A, and F297I/Y337A were examined; but the limiting step in [(C_7H_{13})P═O$(SCH_2CH_2$-$NMe_3)$(Me)]$^+$ degradation/hydrolysis was oxime (HI-6) reactivation. A report by Y.-J. Huang et al. in 2007 involves BChE produced from animal milk and used in animal studies (transgenic mice and goats) for prophylaxis.[240] A 2008 report by A. Saxena focused on human serum (Hu-BCHE) that was tested in the event of whole body exposure to sarin.[241]

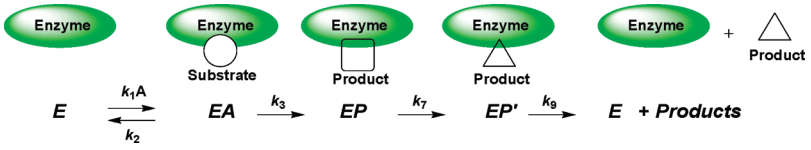
While there has been a variety of reports that attracted the attention of scientists in various disciplines, there have been some nagging technical difficulties in this field. First, it is generally difficult to obtain and purify proteins in sufficient scale for sizable degradation tasks. In some of the reports, it was not possible to lower the toxicity of agent mixtures below satisfactory levels. There is also sometimes mediocre or poor agent−antigen specificity. These challenges can hopefully be met by new approaches for NA destruction and detection in the future.

4.5.4.4. Phosphotriesterase (PTE) and Phosphodiesterase Derivatives and Mutants. Another family of enzymes is the phosphotriesterases and related species. While their natural role and substrates are not clear, they can, nonetheless, degrade various anthropogenic phosph(on)ates. Studies of phosphodiesterase in the context of nerve agents and pesticides involve various reports from the 1980s onward. Some major scientific contributions to the greatly enhanced understanding of PTE come from the career work of F. M. Raushel (Texas A & M University).[242] In a report by V. E. Lewis et al. in 1988, phosphotriesterase from *P. diminuta* is able to specifically degrade the S_P isomer of $(NO_2C_6H_4)$P═S(OEt)(Ph).[243] The effects of phenyl group substitution were also studied; inversion of P-configuration was supported, importantly suggesting the role of nucleophilic water. In 1989, W. J. Donarski et al. studied the effects of phosphotriesterase (*P. putida*) on paraoxon hydrolysis in which the analyte could be modified with (*n*-PrO) or (*n*-BuO) groups.[244] It was confirmed that phospho-mono- and diesters are not acted upon. V_{max} and V_{max}/K_m values were determined for all 16 paraoxon analogues in which the alterations were only at the Ar site. A 1989 study by D. P. Dumas reports a phosphodiesterase (*P. putida*) studied for paraoxon hydrolysis.[245] The value of k_{cat} was determined to be 2100 s^{-1}. Hydrolysis of species such as chlorpyrifos (trade name Dursban), (methyl) parathion, coumaphos, diazinon, fensulfothion, and cyanophos were also measured (Figure 4). The enzyme was inhibited or inactived by metal chelators and inhibitors such as thiols. A preliminary model for active site phosphate hydrolysis was also proposed. S. R. Caldwell et al. in 1991 explored the limits of diffusion for phosphotriesterase (*P. diminuta*) hydrolysis for various derivatives such as paraoxon, etc.[246] A simple mechanism was elucidated, and a cartoon adaptation of it is provided in Scheme 24.

Herein, the k_3 transformation is dependent on the acidity of the phenol; Brønsted analysis supports a very product-like transition state structure. A variety of phenyl group substituents (nitro, fluoro, —C═OR substitutions as well) were included in these studies.

In 1991, S. R. Caldwell et al. also set out to try to describe the active site transition state structure.[247] These studies utilized ^{18}O-labeled substrates and base hydrolysis; enzymatic hydrolysis was measured. Support for an associative mechanism was found. $(EtO)_2$P═O$(OC_6H_4(p$-$NO_2))$ and $(EtO)_2$P═O(carbamoylphenyl) were studied. Primary and secondary ^{18}O isotope effects were determined. A report by J. N. Blankenship et al. involved studying phosphotriesterase inhibition by $(EtO)_2$P═O(O—C≡C—$CH_2(CH_2)_2CH_3$);[248] ketene [O═C═C—$(CH_2)_3CH_3$] formation permits nucleophilic attack in or near the enzyme active site, thus irreversibly "poisoning" the enzyme (99+%). A report by G. A. Omburo et al. involved characterizing and determining the changes upon modification of the Zn^{2+} binding by methods that included Cd^{2+} displacement.[249] Use of ^{113}Cd NMR spectroscopy revealed the presence of *two* signals, signifying two unique environments. A portion of ~2 equiv of metal ions was required. The apoenzyme (full protein devoid of (metal ion) "cofactor(s)") can be formed through treatment with thiol, EDTA (ethylenediaminetetraacetic acid), with the native-type form being regenerated through the addition of M^{2+} ions. A report by J. M. Kuo et al. in 1997 furthered the understanding of the phosphotriesterase structure and function relationship through active site changes;[250] four separate sites that compose the entrance to the bimetallic site were modified (W131F/A, K169M/A/E/R, D253N/A, D301A/N/C). These mutants were

Scheme 24. A Representation and Chemical Mechanism[a]



[a] Adapted partly from a figure from ref 246.

treated with paraoxon. It was concluded that carboxylic acids can sometimes help restore enzymatic activity. Also, in a report by S.-B. Hong et al. in 1997, the putative quinone methide species $[(CH_2{=})(NO_2)C_6H_3({=}O)]$ was proposed to form as a reactive substrate from the aryloxy substituent of precursor $[(BrCH_2)_2NO_2C_6H_3O]P{=}O(OEt)_2$.[251] Also, in 1999 Hong et al. reported that a paraoxon analysis prepared to probe phosphotriesterases revealed dependence on relative steric encumbrance.[252] A comparison of chiral and racemic mixtures revealed that k_{cat} is greater for the (−) enantiomer by 10−100-fold. S_P is always preferred in this reaction. Next, changes in the primary structure of PTE allow for changes in stereoselectivity.[253] Fourteen mutants were produced by site-directed mutagenesis. For instance, G60A (small subsite) decreased k_{cat} in the hydrolysis of R_P enantiomers; this led to a greater selectivity (e.g., 13 000:1) for the S_P analogues. Next, Chen-Goodspeed et al. investigated the possibility of *reversal* of phosphate selectivity.[254] R_P systems indeed can be preferred over S_P through particular single-site mutants. This is possible by placing glycine in the "small subsite" at sites Ile106, Phe132, and Ser308. Also, reducing the size of the large subsite led to reduced activity for S_P type substrates, especially in the case of mutant H257Y. In 2001, M. A. Anderson et al. studied ^{18}O isotope effects using the "remote label method" to establish perturbations of the hydrolysis of $[(EtO)_2P{=}O(OCH_2CH_2NMe_3^+)][I^-]$ and $(m\text{-}NO_2C_6H_4CH_2O)(OEt)_2P{=}O$.[255] The results supported an *associative* mechanism. A report by C. M. Hill et al. in 2003 describes improved rates of degradation for soman, for example;[256] herein they substituted $(O{-}C_6H_4{-}NO_2)$ in place of F−.[257] The rate enhancement increased by a factor of $\sim 10^3$ and was due to a multiple mutation: H254G/H257W (later with L303T); the space allowed by H254G invites coordination of a third metal ion, which dissociates upon coordination of $(^iPrO)_2P{=}O(Me)$. Molecular dynamics simulations and binding free-energy calculations provide a molecular-level explanation for increase in catalytic efficiency of the triple mutant H254G/H257W/L303T toward soman.[258] In 2003, Y. Li et al. reported pairs of racemic species, for example, $(Ph)P{=}O(OMe)(OC_6H_3X\text{-}p\text{-}Y)$ (X = 2- or 3-F or H; Y = $-NO_2$, −CHO, −CN, $-COCH_3$, $-CO_2CH_3$, −Cl), which were treated with PTE with the G60A mutant (25 °C, pH 9.0).[259] This rate increased as a function of pK_a for the $(OC_6H_3X\text{-}p\text{-}Y)$ substituent (pK_a 5.5−9.4). Later, this research was extended by P.C. Tsai et al. to enantiomerically pure chiral nerve agent analogues; several PTE mutants were used.[260] In 2004, S. D. Aubert et al. reported a study of [Cd, Cd] and [Cd, Zn] versions of PTE for comparison to the native [Zn, Zn]; cores were studied with $(EtO)_2P{=}O(OC_6H_4\text{-}p\text{-}NO_2)$ and $(EtO)_2P{=}O(OC_6H_4\text{-}p\text{-}Cl)$.[261] The study supports the conclusion that the α-metal ion bears a hydrolytic hydroxide ion. Enzymatic activity of Co^{2+}-PTE and Cd^{2+}-PTE modifications over the pH range was also studied.[262] In attempts to screen for better catalysts, L. Brizeño-Roa et al. in 2006 conducted high-throughput screening on 12 organophosphorus species. The incorporation of a fluorogenic 3-chloro-7-oxy-4-methylcoumarin group changes its optical characteristics upon dissociation.[263] E. Ghanem et al. reported in 2007 that EA-2192 hydrolysis (Scheme 2) is possible using a glyerophosphodiesterase (GpdQ) (*Enterobacter aerogenes*);[264] 27 species including EA-2192 were analyzed. Also, the paraoxon hydrolysis mechanism was studied theoretically by K.-Y. Wong et al. in 2007. Of note here is a revision of a previous hydrolytic mechanism.[261,265] The $Zn^{2+}\cdots Zn^{2+}$ internuclear distance increases for the transition state enzyme−paraoxon complex. Binding occurs via the phosphoryl [P=O] oxygen with water (hydroxyl group) hosted by the adjacent zinc center (see Figure 12). Recently, molecular dynamics simulations and high-resolution structures of the several PTE mutants, H257Y/L303T (YT), I106G/F132G/H257Y (GGY), and H254Q/H257F (QF), identified the correlations between structural changes in the active site of the enzyme and the kinetic parameters of organophosphate hydrolysis.[266]

Also, E. Dyguda-Kazimierowicz et al. undertook a gas-phase computational study to determine the mechanisms of alkaline hydrolysis.[267] A variety of species was determined theoretically, such as DFP, sarin, paraoxon, parathion, acephate, demeton-S and tabun (see Introduction for structures). The results support an associative reaction; P−F or P−CN cleavage occurs by addition and elimination, whereas P−O and P−S bond cleavages occur by direct displacement.

4.5.4.5. The AChE Type. There has been some research interest regarding AChE-type studies or enzymatic modifications.[268,269] H. A. Berman and his group examined interaction of cholinesterases with organophosphate substrates.[270−272] The chiral nature of these interactions was studied also. Many of these kinds of reports are reviews entailing medical management of agent exposure casualties, which are not covered here.[264]

4.5.4.6. HSA, Paraoxonase, and Fluorophosphatase. Along with AChE-type reports regarding HSA, the paraoxonases and fluorophosphatases can be mentioned as well (*vide infra*). Human serum albumin (HSA) is a ubiquitious protein in the (human) body (~0.6 mM in plasma). There are a few reports detailing how this protein, which transports a variety of natural species and xenobiotics, can serve to hydrolyze organophosphorus agents. A 2008 report by M. A. Sogorb et al. centers around the study of albumin hydrolysis of three separate phosphates.[273] HSA was active in exhibiting "paraoxonase" activity in degrading these species in this order: paraoxon < diazinon < chlorpyrifos-oxon. Next, there is the B. Li et al. 2008 report in which soman was studied.[274] Four indicators of hydrolysis were used: the deactivation of the inherent aryl acylamidase ability of HSA, the production of $[F^-]$, ^{31}P NMR spectroscopy, and mass spectrometry.[274]

Also, there is the serum paraoxonase (PON) families, which contain hydrolytic enzymes toward sarin and soman.[275] This enzyme contains two Ca^{2+} centers; one is considered catalytic,

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

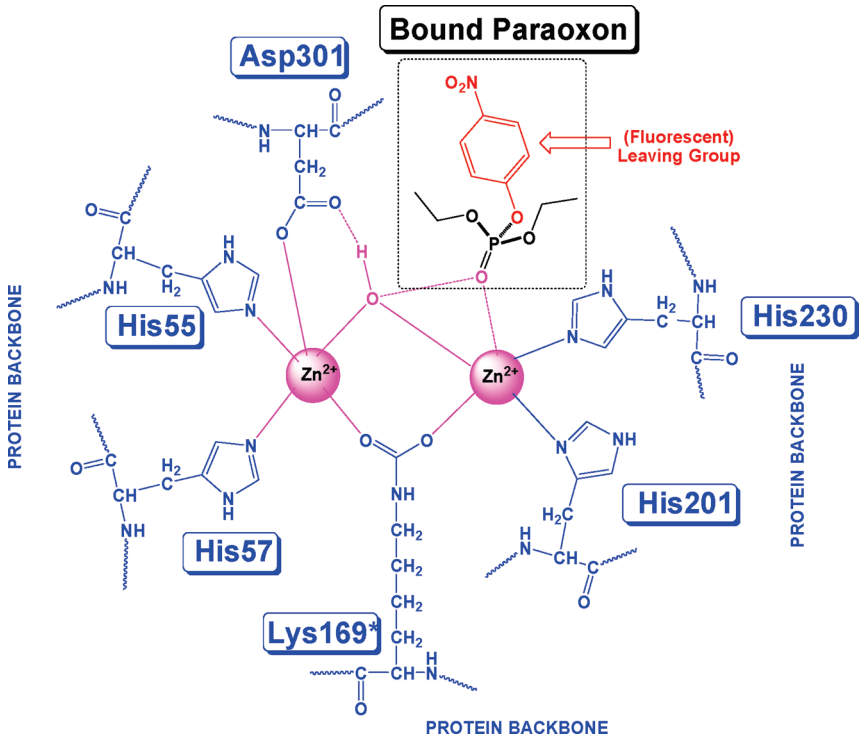


Figure 12. Approximate structure of the Michaelis paraoxon complex for the native dizinc active site of PTE as adapted from K.-Y. Wong et al.[265] Lys169* is a lysine group modified with a carboxylic group.

whereas the other may be considered structural. For structural and sequence information, please refer to other sources.

Mounter and other investigators studied derivatives of difluorophosphatase (DFPase).[276,277] Specifically, for hog kidney (enzymes were extracted from this organ), there was DFPase fluorophosphatase activity with Co^{2+} and Mn^{2+} activation. When *Proteus vulgaris* was studied, *Pseudomonas aeraginosa*: Mn^{2+} was active. A variety of cofactors such as Ca^{2+}, Ba^{2+}, Mn^{2+}, and Zn^{2+} may allow for enzymatic activity; for exact conditions and preparative details refer to papers by Mounter.[277] Other detailed aspects of this sort have also been addressed.[277−279]

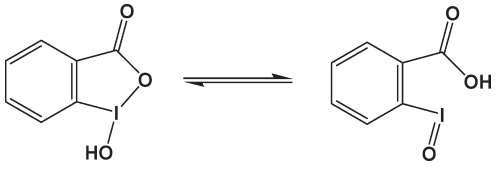
4.5.4.7. Aptamers. The use of aptamers is a recent novel approach for agent pesticide decontamination per a 2008 report by J. G. Bruno et al.[280] These systems are intended as therapeutic agents and rely on guest−host interactions and are products of the systematic evolution of ligands by exponential enrichment (SELEX) process.

4.5.5. Cyclodextrin-Assisted Reactions. Cyclodextrins are able to catalyze the hydrolysis of certain nerve agents such as sarin and soman. Cyclodextrins were first tested against nerve agents in the early 1970s. Van Hooidonk and Breebaart-Hansen (1970) reported the detoxification of sarin through the use of α-cyclodextrin.[281] A decade later it was demonstrated that cyclodextrins are more effective in the inactivation of sarin and soman.[282] The mechanism involving the secondary hydroxyl group(s) of cyclodextrin is identical with the enzymatic mechanism[283] and is illustrated in Scheme 25. Three steps are considered: (i) formation of complex CD−OH*PX, (ii) phosphorylation of cyclodextrin to give phosphorylated CD−OP, and the final step involving (iii) dephosphorylation resulting in a hydrolyzed organophosphonate (P−OH). Rate constants were determined in these hydrolyses of organophosphonates in the presence of cyclodextrin using spectrophotometric methods. Weak detoxifying effects were limited to sarin and soman; tabun and VX were not affected.

Further modification of cyclodextrins was shown to improve catalytic activity. The Cu^{2+} complexes of cyclodextrins that combine the catalytic activity of copper and binding properties of the cyclodextrin enhance the rate of hydrolysis by more than 95 000 and 70 000 times (Figure 13).[284] Another modification involves the iodosobenzoic acid moiety (Figure 13) and was tested against soman and paraoxon.[285,286] Based on this research, a cyclodextrin biological assay (CD-IBA) for high-throughput screening for nerve agent detoxifying materials was developed.[287,288] CD-IBA detoxified tabun demonstrating a broader detoxification effect than for unsubstituted cyclodextrins.

4.6. Halogen as the Nucleophile

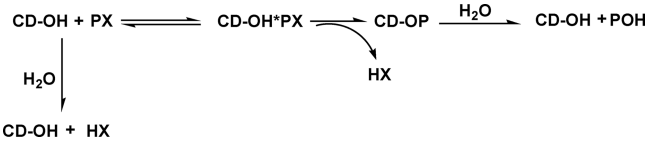
Various halogen-containing systems have been studied in the context of decontamination. A comprehensive *Chemical Reviews* article has been written by Moss.[35] This review constitutes a large part of the career work of Moss in which the chemistry involves the combined attributes of iodosyl benzene and benzoic acid.



4.6.1. Use of BrO_x. Moving up the halogens to bromine, the hypobromite ion (BrO^-), analogous to hypochlorite, is an effective α-nucleophile and has been used to degrade for phosphorus esters. C. A. Bunton et al. reported bis(dialkylamide)hydrogen dibromobromates as a source of BrO^-.[289,290] It is a stable solid

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Scheme 25. Mechanism Showing Interactions of Cyclodextrin CD with Organophosphonate PX



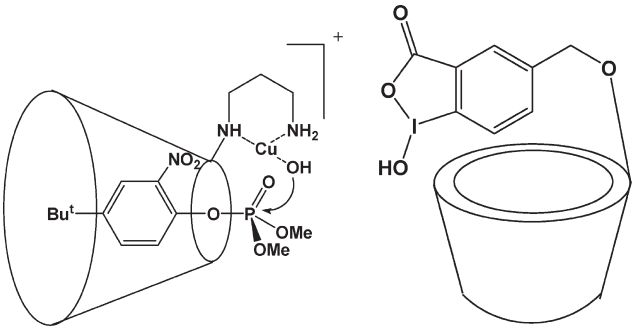


Figure 13. (left) Hydrolysis of phosphate with Cu^{2+} complex of modified cyclodextrin. Adapted from ref 284. (right) Structure of CD-IBA.

and gives BrO^- and HOBr under aqueous alkaline (pH 10−11) conditions. The nucleophilic substitution reaction of BrO^- is shown in Scheme 26.[289] Treatment of 4-nitrophenyl phosphonates and phosphates, simulants for the phosphonofluoridate nerve agents, shows rapid changes at an absorbance of 420 nm indicating simulant decomposition.

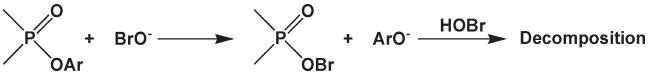
4.6.2. Use of Other Halogens. Alumina-supported fluoride reagents are used for the hydrolyses of VX, GB, and HD with good results.[291] KF/Al_2O_3 solid reagent can quickly hydrolyze VX by P−S cleavage to the nontoxic species EMPA ($t_{1/2}$ = 0.1−6.3 h) and toxic desethyl-VX, also known as EA 2192, by P−O cleavage ($t_{1/2}$ = 2.2−161 h). The latter can be further hydrolyzed to nontoxic MPA ($t_{1/2}$ = 2.2−161 h). In the same manner, HD is hydrolyzed to nontoxic thioxane and TDG, while GB produces nontoxic IMPA. These hydrolysis reactions (see Scheme 27) are monitored by ^{31}P MAS NMR spectroscopy (see section on NMR spectroscopic characterization). Also, zeolitic AgF powder can be used for the destruction of VX through desulfurization.[292,293]

4.6.3. Use of Group 13 Chelates. The dinuclear boron compound Salpen(^{t}Bu)$[BBr_2]_2$ was synthesized by D. A. Atwood and co-workers.[294,295] This compound is able to cleave the C−O bond in phosphate esters. Many phosphate esters with different alkyl chain length are tested with compounds and all show good activities (>60% conversion by ^1H NMR spectroscopy). As products, alkyl bromides and chelated boron phosphates are formed.

4.7. Surface Chemistry

Heterogeneous surface topics pertinent to organophosphonate detoxification were previously reviewed in 1988. A variety of species were treated with emphasis on (i) oxidation, (ii) dealkylation, and (iii) hydrolysis.[33] Importantly, while there are many reports dealing with solids with adsorption, we will focus on reports that involve bond cleavages.

Scheme 26. Decomposition of Phosphinate with BrO^-[a]



[a] Adapted from ref 289.

4.7.1. Bare Metals and Solid Nanoparticles. A variety of *elemental* metallic crystal facets have been the sites of interest for a group of studies. Here we recount a series of reports on "bare" metal surfaces that involved the use of DMMP. Mo(110) was the first surface studied.[296] In 1985, R. I. Hedge and co-workers reported Rh(100) treated with DMMP in which there was also evidence of DMMP desorption.[297] A carbon coating was also tested to determine that it inhibits agent activation. Next, there were also studies by X. Guo et al. of DMMP decomposing on Ni(111) and Pd(111).[298] Phosphorus from the agent forms a layer on the metallic surfaces removable by treatment with O_2 in the case of Pd, but not with Ni (at 1075 K).[296] The decomposition reaction for Pd(111) is shown in eq 5 in which the adsorbed materials may be liberated at higher temperatures and with oxidation:

$$\mathrm{DMMP} \rightarrow \frac{7}{2}\mathrm{H_2(g)} + 2\mathrm{CO_2(g)} + \mathrm{H_2O(g)} + \mathrm{P(adsorbed)} + \mathrm{C(adsorbed)} \quad (5)$$

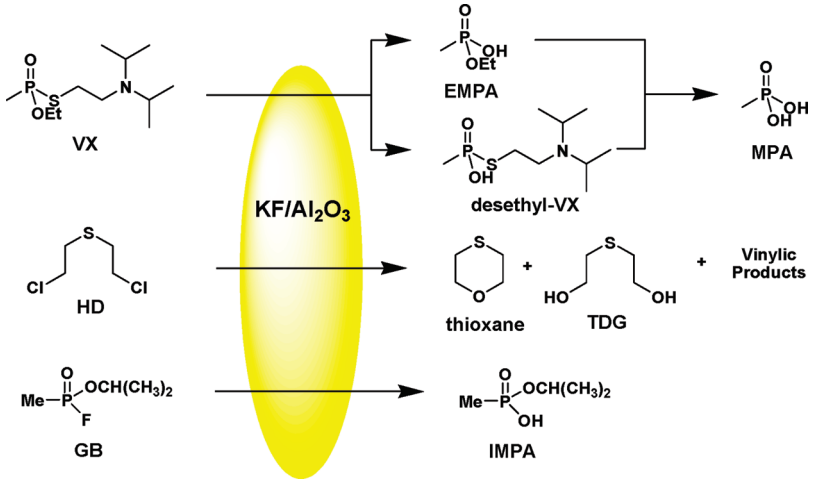
A comparison with Mo(110) indicates a more facile oxidative removal of phosphorus at ∼900 K and, thus, for earlier transition metals.[296] Next, a Pt(111) surface in the form of Pt crystal was studied by M. A. Henderson et al.[299] It was determined that DMMP decomposition occurs above 300 K to give P and C deposition. Under heating, $[PO-CH_3]$ bond cleavage occurs, followed by $[P-OCH_3]$; also $[P-CH_3]$ bond cleavage occurs in higher temperature regions. Also DMMP activity on a platinum wire was studied by C. S. Dulcey et al. in 1985.[300]

In terms of an atomic level understanding, a greatly detailed report is provided by M. A. Henderson and J. M. White.[299] In previous related studies, the role of the Pt in catalytic deactivation of organophosphorous compounds could not be determined. This paper proposes a molecular surface binding model supported by various data, including high-resolution electron energy loss (HREEL) spectroscopy and Auger electron (AE) spectroscopy. Importantly, the generation of H_2 and CO are noteworthy. Mono- and multilayers were considered; the monolayer model rationalizing the reported loss of H_2 and CO is illustrated in Scheme 28.

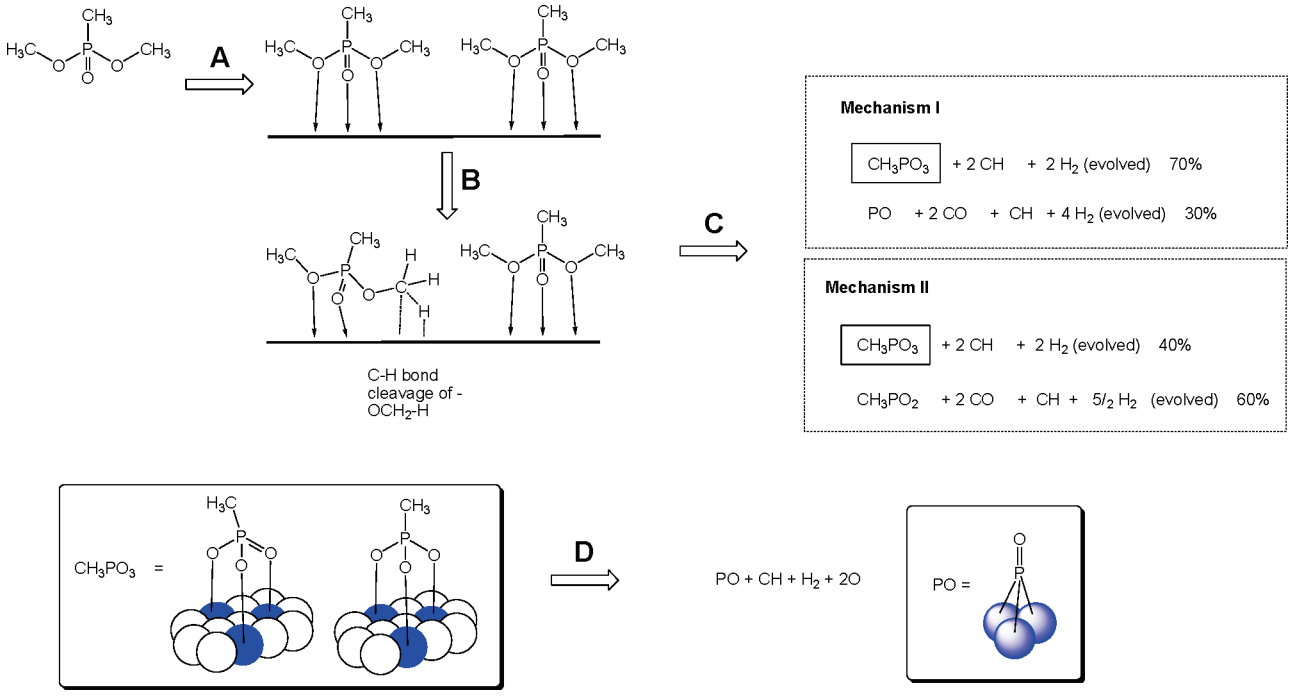
A great deal of effort involved interpreting infrared spectra, which could probably be processed more efficiently now than in the 1980s, which was when much of this work was undertaken. A sample IR spectrum of various reactant (DMMP) bands and their changes is shown in Figure 14. The arrows show signal intensity changes as a function of change in temperature (298 → 440 K). This sample involved preadsorbed DMMP onto Y_2O_3 particles that were 6 nm in dimensions. The challenge here, and that which continues, is underscored by the build-up of phosphorus on the surface.

4.7.2. Metal Oxides. Metal oxides in all forms and formulations constitute a large class of decontamination materials; many reports appear in *J. Phys Chem.* and *Langmuir*, among others. One major contributor here has been G. W. Wagner. The benefits of metal-oxo species are their robustness and high activity. These species are sometimes studied in semiconducting applications.

Scheme 27. Hydrolysis Reactions of VX, HD, and GB with the KF/Al_2O_3 Reagent



Scheme 28. Proposed Preliminary H_2 Generation Pathway of DMMP on the Sub-monolayer Surface Coverage (Low Coverage) in Which Molecules Are Not Affected or Influenced by One Another[a]



[a] Adapted from M. A. Henderson et al.[299]

These materials are refractory, allowing for high-temperature applications. From this work as well, it has not been abundantly clear which mechanisms are at play on the molecular level at the surface. Since surface coverage and mechanism are of course at the heart of these species, these will be surveyed and analyzed below. They are also of current commercial interest. Recently, NanoScale Corporation (http://www.nanoscalecorporation.com) was awarded a large U.S. Army contract to supply nanoscale metal oxide powder decontamination kits for soldiers in the field.

4.7.3. Representative Elements. Several reports from the 1980s deal with DMMP vapor (P═O (gas phase) $\upsilon = 1260\ cm^{-1}$) on surfaces involving oxidized iron,[302] Al_2O_3,[303] SiO_2, and α-Fe_2O_3.[304] The K. J. Klabunde research group extensively studies decomposition of phosphorus compounds by magnesium oxide surfaces.[53,305−307] A report by Rajagopalan and co-workers in 2002 describes the use of nanocrystalline MgO[308] in the "destructive adsorption" of paraoxon, $(^iPrO)_2P{=}O(F)$, and $(CH_3CH_2O)_2P{=}O(CH_2SC_6H_5)$. The cleavage of P−OR and P−F bonds occurred, as supported by spectroscopy; no evidence for P−C bond cleavage was obtained. The use of mixed "intermingled" alkaline earth oxide−alumina particles (e.g., $MgO-Al_2O_3$) in an aerogel-type medium was also reported.[309] The aerogel method was intended to give higher dispersion. The particle surface area decreased from

dx.doi.org/10.1021/cr100193y |Chem. Rev. 2011, 111, 5345–5403

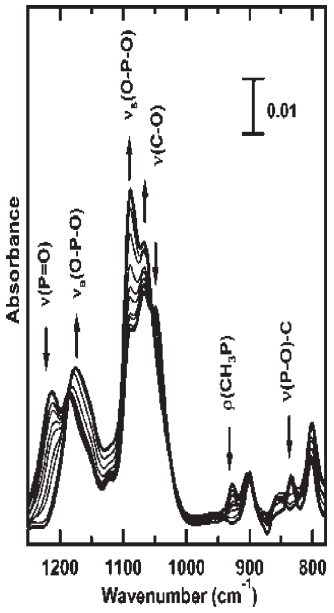


Figure 14. The IR spectroscopic region showing growth and diminution of various vibrations bands assigned to features of phosphonate species. Copied directly from ref 301.

Mg^{2+} down to Ba^{2+} and reactivity was reasoned by cation size. Paraoxon was degraded as conveniently observed through the diminution of the phenyl-based absorption band centered at 267 nm; the O−Ph substitutent and the phosphonic acids were subsequently adsorbed. Wagner also studied the MgO system in a 1999 report;[310] VX was studied, but EA-2192 was not detected.

Here, as with other studies, the TEM technique allows for the comfirmation of a portion of the sample but does not help significantly in improving a mechanistic understanding. Recently, new MgO particles (MS284) were prepared with better performance in the destruction of nerve agent simulants.[311]

There have also been some studies related to calcium oxide systems. CaO in the form of nanocrystals with Fe_2O_3 was studied.[312] CaO can be a support for Fe_2O_3, a species coated with Fe_2O_3, or a stand-alone degradation medium. CaO was able to degrade DMMP and was also studied as degradative nanocrystals with VX and GD analytes.[313] This decomposition gives surface-bound adducts of ethyl methylphosphonate from VX and pinacolyl methylphosphonate from GD.

Aluminum-containing materials, namely, alumina, serve in degradation in some reports. Alumina itself also plays the role of a substrate in combination with other metal oxide systems. G. W. Wagner and co-workers studied a variety of agents, GB, GD, and VX, with Al_2O_3.[314] Here, aluminophosphates can be formed (Scheme 29); agent degradation was also found to occur in the "core" of the alumina particles. Density functional theory (DFT) was applied to study environmental effects such as surface hydroxylation and photoexcitation in line with exposure to terrestrial solar radiation in the adsorption of DMMP, sarin, and VX on γ-Al_2O_3.[315] It was established that for all three species, adsorption on an OH-free surface occurs via an $Al(T_d)$—O═P dative bond to an unsaturated tetrahedral $Al(T_d)$ site. Impregnate Al_2O_3 nanoparticles were produced and kinetics of adsorption of DCP and sarin was monitored.[316]

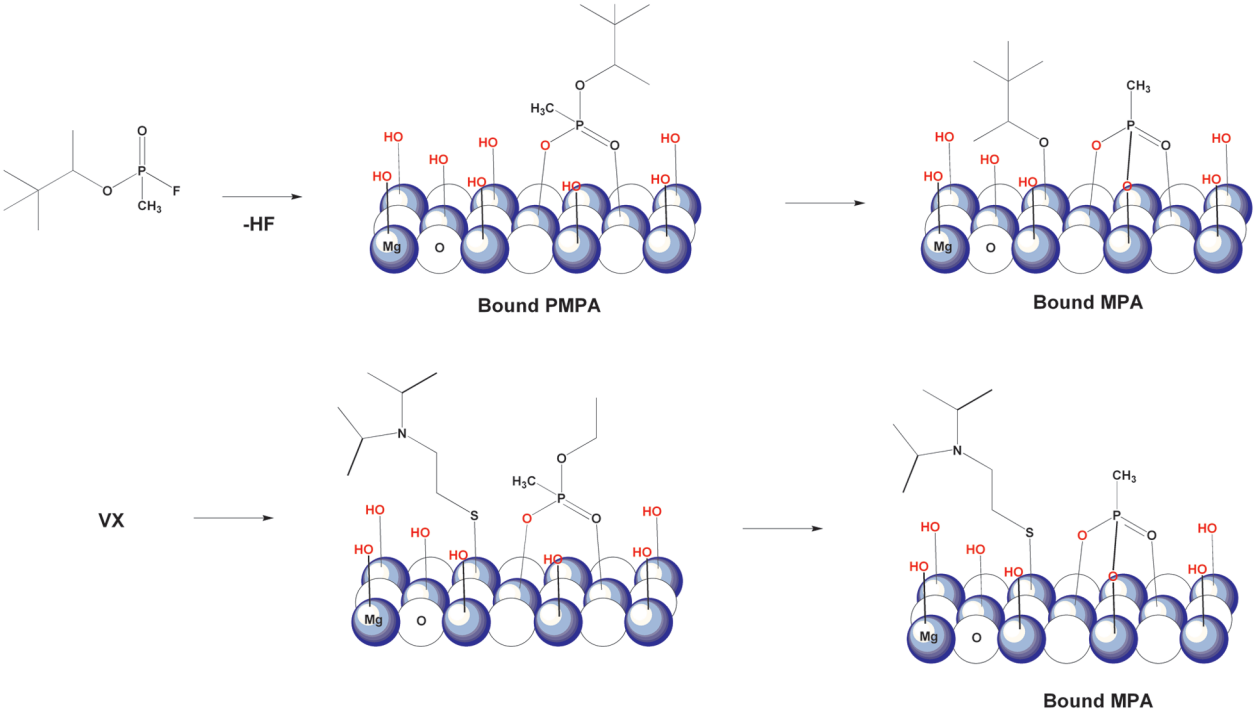
Certain discrete models of magnesium oxide particle systems that were explored experimentally have also been treated theoretically in order to gain a better understanding of the mechanism. In particular, Mg_4O_4 and $Mg_{16}O_{16}$ were used in a theoretical modeling study, and both Ca^{2+} and Mg^{2+} oxide surfaces and DFP ($(^iPrO)_2P$═O(F)) have been the subject of calculations.[317] Mg^{2+} was determined to bind the analyte through the phosphoryl oxygen more strongly. For GB, adsorption is preferable on the surface of octahedral Al hydroxide rather than on the surface of tetrahedral silica. Sarin was studied on dickite, $Al_2Si_2O_5(OH)_4$.[318−320]

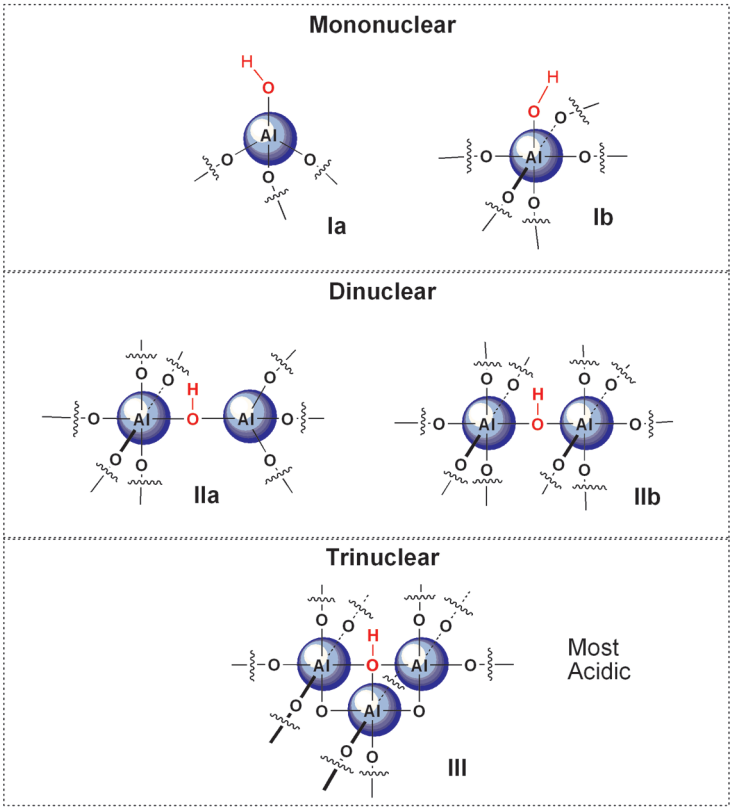
Silica has also been studied in OP degradation. The silica edges are thought to have OH-functionalized surfaces. First, DMMP was examined.[321] TCP, MDCP, (sarin), DMMP, and TMP were assessed to have, in the order listed, a decreasing adsorption strength. Sarin is placed in parentheses because its data are based on calculations. Herein, the binding is not via conventional phosphoryl oxygen adsorption but rather by hydrogen bonding, as shown in Figure 15. J. Quenneville et al. examined the interaction of DMMP with amorphous silica as a function of surface hydroxylation density (number of OH groups in 1 nm^2 of silica surface) by using molecular dynamics simulations in conjunction with the ReaxFF reactive force fields.[322] Van der Waals interactions, hydrogen bonding, strong covalent bonding, and even DMMP fragmentation were observed in surfaces with different OH densities. S. M. Kanan et al. also previously reported an infrared study to assess the hydrogen bonding capabilities of the series of analytes, which vary in their number of hydrogen bonds with the surface.[323] Agents were found to desorb intact, allowing for a return of the original surface; this reversibility is important in sensing. DMMP in particular can be selectively adsorbed out of a methanolic gas stream.

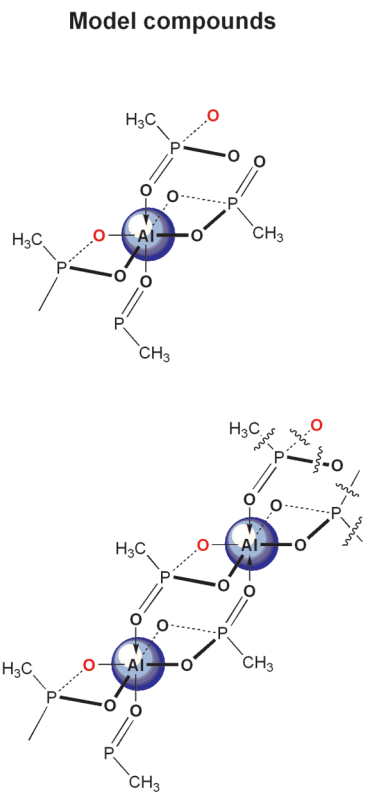
Of these representative reports taken together, those by G. W. Wagner and co-workers stand out as comprehensive. They describe inexpensive and versatile materials (e.g., MgO and Al_2O_3) that provide for some degree of atomic-level understanding.[310,314] A scheme for agent degradation at the MgO surface and related reactivity appears in Scheme 29.

4.7.4. d-Block (Groups 4−10). The oxo species of d-block elements are also involved in organophosphonate studies. In 2001, Kim and co-workers reported TiO_2, in the form of a powder, in the adsorption of DMMP, $(MeO)_2P$═O(H), and $(MeO)_3P$═O using IR spectroscopy.[324] Next, there are TiO_2-based catalysts that were investigated with DMMP and TMP in which the surface was modified by Pt and Pd.[325] Separately, DMMP was tested at the (110) surface of TiO_2; a P−OMe stretch was assigned to an adsorbed DMMP molecule.[326] Molecular imprinting on titanium dioxide was found to be very effective in the degradation of DIMP.[327] The high activity of TiO_2 under UV-light irradiation was observed in photocatalytic decomposition of DMMP.[328] Mesoporous titania containing gold nanoparticles was prepared as a photocatalyst for the decontamination of soman.[329,330] The catalyst operates under ambient light and is considered environmentally friendly. Attenuated total reflection−infrared Fourier transform spectroscopy (ATR-FTIR) can be used in the study of adsorption and photocatalytic degradation of sarin on powdery TiO_2 film.[331] S. M. Kanan and co-workers reported an IR spectroscopic study of WO_3, treated with DMMP, TMP, and MDCP.[332] It was found that MDCP can be hydrolyzed after adsorption of the species through its O═P bond. The species is then hydrolyzed by a water molecule that was adsorbed as part of a water layer. Z. X. Lu et al. reported DMMP adsorption on monoclinic-WO_3 nanoparticles; DMMP was analyzed.[333] It was found that for DMMP, the

Scheme 29. (top) Idealized MgO Surface and the Degradation of Sarin, a Helpful Model for Understanding Al_2O_3, Degradation of GD and VX on Surfaces, and the Variety of Alumina Surfaces; Hydrolysate Relative Position Is Not Confirmed;[a] (bottom) Illustration of the Different Kinds of Alumina Sites for Hydroxyl Groups[b]







[a] Adapted from refs 310 and 314. [b] Adapted from a paper by G. W. Wagner and coworkers.[314]

$O-CH_3$ stretches at 1042 and 1069 cm^{-1} are unchanged, whereas the P═O stretch is assigned to the band at 1209 cm^{-1}, supporting phosphoryl binding. C. P. Tripp also determined this with alcohol interferents.[334] C. S. Kim et al. also studied WO_3

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

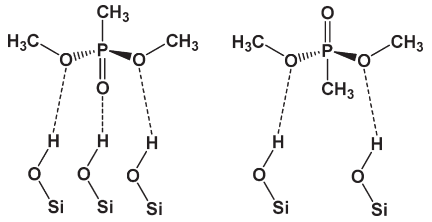


Figure 15. Different hydrogen bonding modalities for DMMP at SiOH groups. From ref 323.

powders and relied on IR spectroscopy.[324] Mesoporous manganese oxide nanobelts were synthesized, and kinetics of decomposition of sarin, sulfur mustard, and chloroethylethyl sulfide were investigated.[335] Zirconium-doped nano oxides of Fe, Al, and Zn increase the rate of degradation of soman and VX. The enhancement occurs due to an increase of surface area after addition of Zr^{4+}.[336] There were also studies of silver oxide and vanadium oxide surfaces.[337−339]

4.7.5. Solid Metal Oxides of Group 3 and the Lanthanides. Lanthanides hold promise in many related applications because of the variety of common forms of these materials. Reports by W. O. Gordon detail DMMP decomposition through the use of Y_2O_3 nanoparticles. This reaction is stoichiometric at RT.[301] With smaller average particle sizes, there was more degradation; this is in accord with not only greater surface area, but also perhaps an increase in the number of defects. Also there was evidence for P−O−Me bond cleavage. Agent degradation was supported by RAIR spectroscopic and XPS data indicating changes after treating with DMMP. There are some related studies of phosphates with lanthanides such as a report by C. J. Hartzell et al.[340] Obviously, there are fewer reports here than for the d-block, but a closer look at the yttrium example is interesting because it is classified as both a d-block metal and a rare earth metal (Scheme 30).

4.7.6. Porous Silicon and Related Systems. There are some reports involving porous silicon in devices. Two recent reports come from the research efforts of S. Jang et al.[341,342] First, a rugate porous silica architecture was studied with DMMP, DCP, and DEEP; TEP was also studied.[342] Next, porous silicon was used to effect the detection of DMMP; a double reflection interferometer was used.[342] Diethylethylphosphonate, $(EtO)_2P{=}O(Et)$, was also tested. Next, M. J. Sailor and co-workers reported a "humidity-compensating" sensor; it was tested to discern between water vapor and DMMP. Also, responses for toluene, heptanes, and ethanol were collected.[343] Porous silicon surfaces are still new and being pursued as decontamination/detection platforms.

4.7.7. Zeolites. Some researchers have investigated aspects of zeolites in terms of organophosphonate sensing or decontamination. Different from simpler metal-oxo species, zeolites are well-known for their particles of variable size and their distinct internal channels. This gives an excellent overall agent contact area considering the decrease in average particle size and boost from internal surface binding. In 1992, W. T. Beaudry and co-workers prepared resins that were used to degrade DMMP; $(p\text{-}NO_2{-}C_6H_4)P{=}O(OPh)_2$ was also studied.[344] Through these adsorptive studies, a sorptive site, attributed to the uptake onto the surface, and a less-strongly adsorbing secondary low pertaining to an ammonium hydroxide site were discovered. Sodium- and silver(I)-exchanged zeolites were also studied by G. W. Wagner for the detoxification of VX.[293] VX and $[(EtO)(EtS)P{=}O(Ph)]$ (DEPPT) were found to degrade via [P−S] bond cleavage to give $(EtO)(HO)P{=}O(Me)$ with faster action observed for Ag over that for Na. A secondary product, $(^{i}Pr_2NCH_2CH_2O)(OEt)P{=}O(Me)$ (QB), is proposed to form from a phosphonic acid−Ag complex. Previously, a AgF-impregnated sorbent was reported to degrade VX. Detailed mechanisms based on this paper are provided below in Scheme 31.[260] The silver zeolite is depicted as desulfurizing VX. Then, DMMP was also detected by zeolite films of ZSM-5 (aluminosilicate zeolite).[345] This zeolite was also modified with Ag^+ sites. Next, nanocrystalline sodium-zeolite (average particle diameter ∼30 nm) was studied by K. Knagge and co-workers.[346] Here, the adsorption and degradation were monitored by IR and magic angle spinning (MAS) NMR spectroscopy. Smectites (generally species of the formula $(Ca,Na,H)(Al,Mg,Fe,Zn)_2(Si,Al)_4O_{10}(OH)_2\cdot xH_2O$) were also treated with DMMP.[347] As with other studies, the M^{n+} complex (e.g., Mg^{2+}) of phosphonate was formed for use as a model complex.

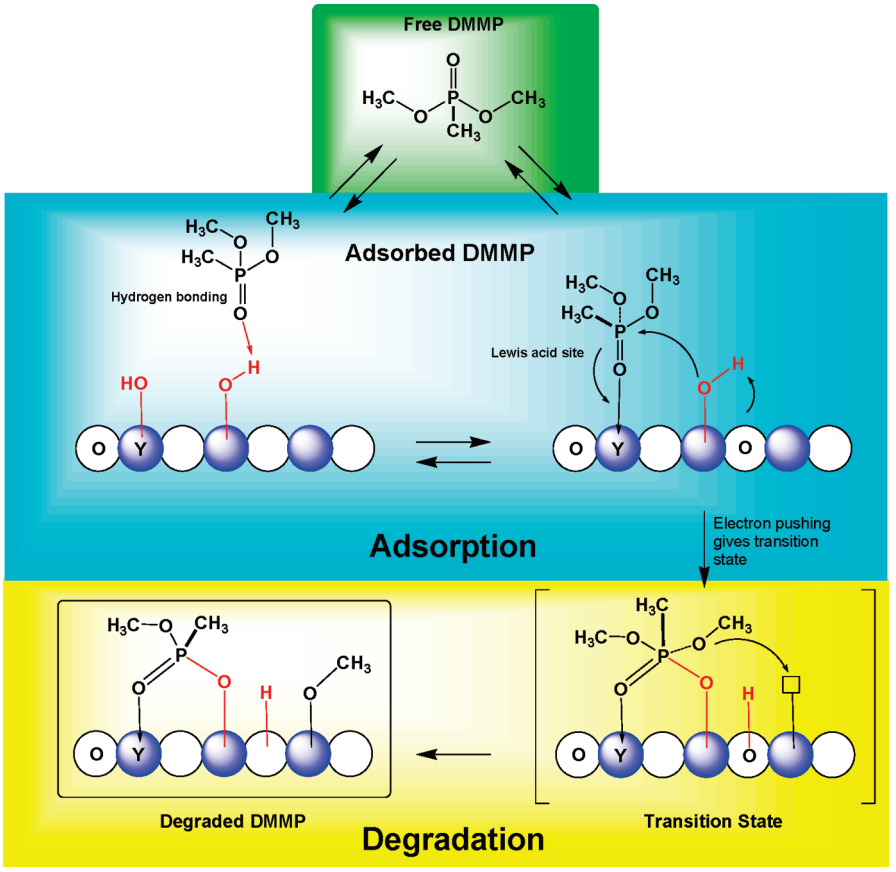
There are also some biochemical and animal model studies, as well as those pertaining to certain kinds of microorganisms, that help gauge the usefulness of zeolites as active sorbents *in vivo*.[348] Bacteria and protozoa (rumen) were studied with and without clinoptilolite-containing material (clinoptilolite = $(Na,K,Ca)_{2-3}Al_3(Al,Si)_2Si_{13}O_{36}\cdot 12H_2O$). There was a report involving the decomposition of DMMP to $(HO)_2P{=}O(Me)$ when exposed to sodium zeolite.[349] Faujasite is $(Na_2,Ca,Mg)_{3.5}Al_7Si_{17}O_{48}\cdot 32H_2O$. Zeolite tuff (61% clinoptilolite) was studied on the effect of VX in a rat model.[350] The rat was treated (peroral administration) with VX in which clinoptilolite was the main protective ingredient. In this model study, various organs were monitored for their AChE activity with greatest adverse effects being found in the stomach, brain, and liver. *In vivo* zeolite capabilities were also determined using a sheep model.[351] Here, the zeolite was administered together with a portion of charcoal. Animal agent poisoning criteria could be determined from the extent of mortality in these animals. It was concluded that zeolites while naturally offering some prophylactic effect based on the animal studies, may pose difficulty in adaptation for human study and use.

4.7.8. Comparative IR Data. Any continuing or new practitioners exploring new chemical systems in agent degradation will most likely require comparative normative IR spectral data on agents and simulants. Such data is provided for the ubiquitous model system DMMP, see Table 2.

4.8. Other Types of Systems

Outside of the types of systems listed here, there are other reports including magnetic nanoparticles. A. Bromberg and co-workers studied catalytic magnetic nanoparticles.[353] These nanoparticles were composed of magnetite (Fe_3O_4) and either a monomer or a polymeric derivative of 2-pralidoxime. There have been other techniques reported as well, such as those dealing with plasma, electrochemical oxidation, and solvated electrons. Plasmas (ionized gas or gases) have been reported in studies that focus on agent degradation.[15] There have been reports of a plasma torch as well.[15] Separately, there is an agent decontamination chamber developed by scientists at Los Alamos National Laboratory.[354] There have also been some studies investigating the practicality of using chemical species generated electrochemically for agent decontamination. An independent e-chem section (*vide infra*, Section 7.9) will detail specifics of these

Scheme 30. Hydrolysis of DMMP on the Yttria Surface [a]



[a] Adapted from ref 301.

reports. There was an electrochemical formation of iodine reported by W. Xie in which $(EtO)_2P{=}O(CN)$ was detected at a solution concentration of 2×10^{-6} M.[355] The use of solvated electrons in synthesis has also been mentioned.[15] The use of the common NH_3/Na solution for the destruction of agents has been described in the patent literature.[356]

5. DECONTAMINATION

The objective of agent decontamination involves various generalized methods and strategies. Decontamination and degradation are differentiated here. Degradation implies discrete (molecular level) bond cleavages that afford products that may still be toxic.

5.1. Overview: Ability to React with All Types of Agents, Ease of Application, and Compatibility with Treated Objects

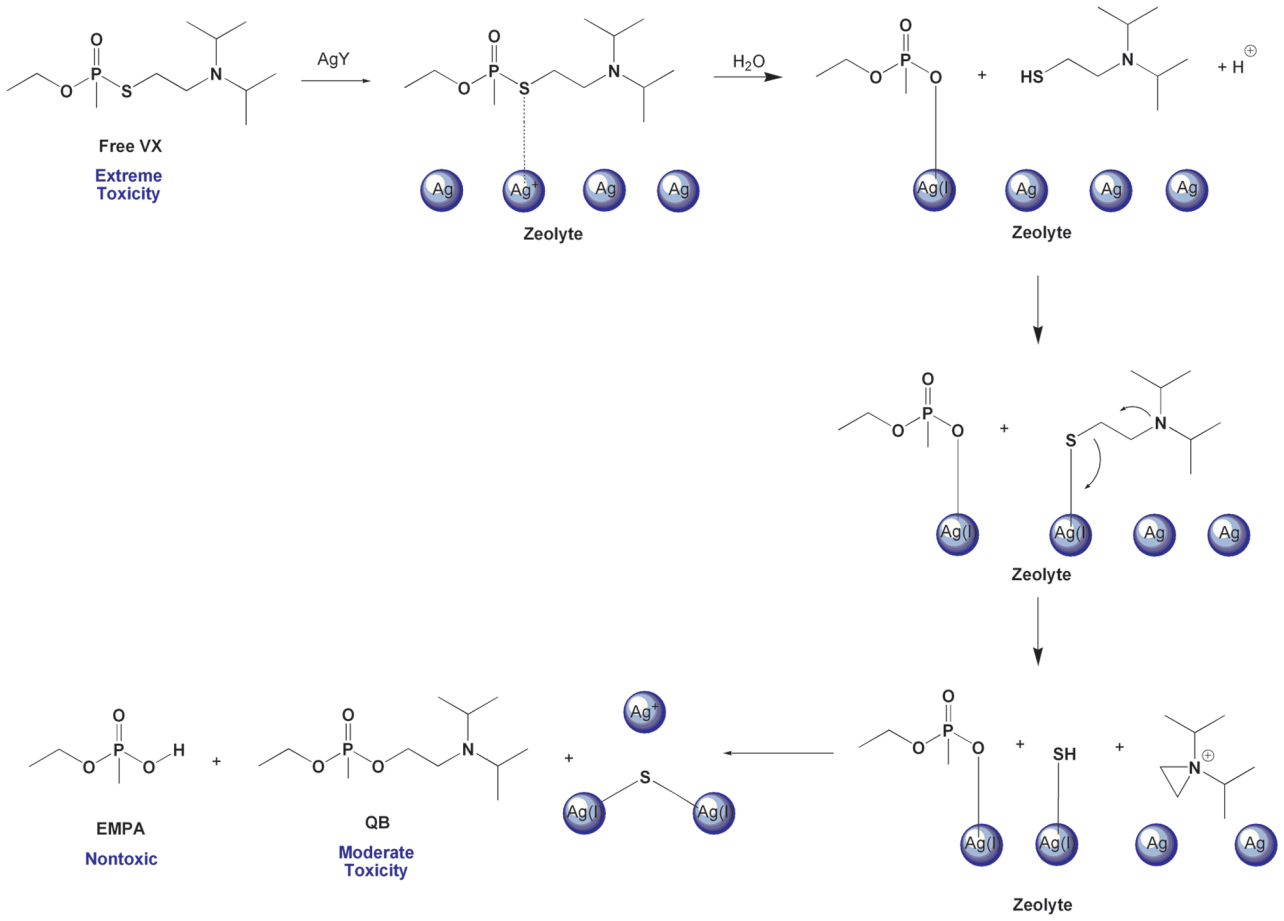
There are many research papers and patents concerning the decontamination of nerve agents that detail various formulations of solutions, microemulsions, bled compositions, fibers, and enzymes.[357−368] Decontamination is defined as the process of removing or neutralizing chemical agents from people, equipment, and the environment and can be grouped into two main categories: (i) physical and (ii) chemical removal of the contaminant. In this section, we briefly describe several decontamination systems and applied techniques. The chemical aspects of decontamination are discussed in section 4 (Decomposition Reactions section). Early decontaminants used were bleaching powders such as HTH (high test hypochlorite), STM (super tropical bleach), Dutch powder, ASH (activated solution of hypochlorite), and SLASH (self-limiting activated solution of hypochlorite).[2] Both G and V agents undergo bleach-mediated decomposition (See section 4). Decontamination proceeds rapidly in a few minutes to nontoxic products. But, the (bleach) decontaminant must be prepared fresh, and its use on a large scale is required for complete deactivation of agent. Moreover, bleach is corrosive to many surfaces.

In 1960, another standard decontaminant was adopted. Decontamination solution 2 (DS2) is a nonaqueous liquid composed of 70% diethylenetriamine, 28% ethylene glycol monomethyl ether, and 2% sodium hydroxide.[369] The active component is the conjugate base $CH_3OCH_2CH_2O^-$, which allows NAs to form their diesters and further degrades them to the corresponding phosphonic acids. This decontaminant possesses long-term stability and a large operating temperature range (−26 to 52 °C). DS2 is noncorrosive to most metals, but it reacts with paints, plastics, and leather materials; therefore, the contact time is limited to 30 min, whereupon rinsing with large amounts of water is required. A greater extent of NA loss occurs when application is followed by a scrubbing action. DS2 is also corrosive for the skin, so chemically protective gloves and respirators that include eye shielding are required during handling. DS2 is flammable and cannot be used with bleach or other strong oxidizing agents such as calcium hypochlorite; doing so may cause the mixture to spontaneously explode.[131,370]

There are several decontamination kits, developed by the U.S. Army.[369] The M258 kit, as well as the M258A1 and M280

dx.doi.org/10.1021/cr100193y |Chem. Rev. 2011, 111, 5345–5403

Scheme 31. Degradation of VX[a]



[a] Adapted from ref 293.

Table 2. Common IR Spectroscopic Features (Frequencies, cm^{-1}) in or on Nonreactive Media[a]

vibrational modes /media	hexane	CCl_4	KBr	SiO_2
$\nu(CH_3P)$	2992	3006	3003	3006
$\nu(CH_3O)$	2957	2961	2956	2961
$\nu(CH_3P)$	2926	2935	2925	2935
$\nu(CH_3O)$	2852	2857	2855	2857
$\delta(CH_3O)$	1467	1462	1487	
$\delta(CH_3O)$	1452	1448	1457	
$\delta(CH_3P)$	1421	1417	1423	
$\delta(CH_3P)$	1314	1319	1314	
$\nu(P{=}O)$	1246	1251	1252	
$\rho(CH_3O)$	1185	1186	1186	
$\nu(CO)$	1061	1066	1061	
$\nu(CO)$	1033	1039	1040	
$\rho(CH_3P)$	914	915	917	
$\nu(PO_2)$	820	895	821	
$\nu(PO_2)$	789		794	
$\nu(PC)$	711		712	

[a] Adapted from ref 352.

skin decontamination kits, consist of two packets, one containing a towelette prewetted with a solution of 10% phenol, 72% ethanol, 5% sodium hydroxide, 0.2% ammonia, and 12% water by weight. Another towelette is impregnated with chloramine-B and accompanied by a sealed glass ampule filled with a 5% zinc chloride solution. The towelette is wetted with the solution from the ampule. Zinc chloride helps maintain an aqueous pH of 5−6 in the presence of chloramine-B, which would otherwise bring the pH to 9.5. These kits are effective against G agents (via nucleophilic substitution at the phosphorus). VX reacts with solutions contained in the kits; greater decontamination occurs through a mechanical wiping action that facilitates agent solubilization. The decontamination kits M291 and M295 contain nonwoven fiber pads filled with resin mixture composed of absorptive resin based on styrene/divinylbenzene. They provide a high surface area with carbonized macroreticular styrene/divinylbenzene resin, cation-exchange sites (sulfonic acid groups), and anion-exchange sites (tetraalkylammonium hydroxide groups). The primary effectiveness of kits depends on the physical removal of the agents by wiping, as hydrolysis with the reactive resin is still slow.[369]

Reactive skin decontaminant lotion (RSDL) was developed in Canada by Purdon's team at Canada's defense department and contains an alkali metal salt of phenol, acetone oxime, acetophenone oxime, 2,3-butanedione monoxime, and a solvent, such as tetraglyme.[371,372] The system is effective against V- and G-type NAs.

Since chemical agents have limited water solubility, both micelles and emulsions have been investigated as potential liquid

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Table 3. Some Physical Properties of Nerve Agents.[a]

nerve agent	vapor pressure (mm Hg) at 20 °C	volatility (mg/m^3) at 25 °C	solubility (g/100 g) at 25 °C
sarin	2.10	16400−22000	miscible
soman	0.40	3060−3900	2.1 (at 20 °C)
tabun	0.037	576−610	9.8
VX	0.0007	10.5	miscible at <9.4 °C, sparingly miscible at 25 °C

[a] Adapted from ref 376. Solubility is in water.

decontamination media. When a chemical agent encounters a microemulsion system, it is partially dissolved into the organic phase of the microemulsion. The agent reacts with the water-soluble decontaminant at the surface of the organic phase. The rate of decontamination depends on the size of the microemulsion particles; smaller particles allow for a faster reaction. An example of a microemulsion system, developed by Germany, is decontamination system *C8*. It contains 15% tetrachloroethylene (C_2Cl_4) which serves as the continuous phase (water is dispered in organic tetrachloroethylene liquid system), 76% water, 1% anionic surfactant, and 8% $Ca(OCl)_2$.[2,370] *C8* penetrates into dry paint without surface disintegration. It is not corrosive, and when sprayed it forms a thin film on the surface to allow sufficient time for detoxification. Another example of a microemulsion is system MCBD. The microemulsion medium is 60% water, 7% tetrachloroethylene, and 28% CTAC (*n*-cetyl trimethylammonium chloride), and it contains a cosurfactant, $(nBu)_4NOH$. The reactive part of this system is 4% Fichlor, 0.1% sodium 2-nitro-4-iodoxybenzoate (IBX), and sodium borate. IBX is a nucleophilic catalyst for the hydrolysis of agents. Borate buffer is required to keep the IBX active.

There have been some efforts made toward the lab-on-a-chip, as well as fiber optics.[373] The first technique is based on microfluidics that treat sarin. There have been a limited number of endeavors involving fiber optics as well.[374]

6. AGENT FATE AND DISPOSAL

Information on the properties and environmental impact and fate of nerve agents is important in terms of safety and adequate remediation in nerve agent stockpile destruction, and the cleanup of nonstockpile sites and facilities associated with production, storage, and testing.

Nerve agents are generally not considered very persistent,[375] although their degradation products can be quite persistent in the environment. Some of the latter should be considered seriously because of their high toxicity. Some agent physical properties are given in Table 3.[376] In general, V agents have greater persistence than G-series agents. Among several degradation processes, determining the fate, such as sorption, volatization, photolysis, hydrolysis, oxidation, microbial degradation, and hydrolysis are the most relevant.

Nerve agents are liquids at room temperature, and their volatility is low. The most volatile, sarin, has a vapor pressure and volatility of 2.10 mm Hg and 22 000 mg/m^3, respectively. V agents are less volatile than G agents and tend to be persistent on surfaces, whereas the G agents present more of a vapor hazard. Estimated volatization rates for sarin and VX and their degradation products indicate that only the volatization of sarin may be significant relative to the rates of hydrolysis for these compounds.

6.1. Indoor

Several studies related to indoor deposition and desorption processes of nerve agents were conducted.[377−379] Theoretical models were developed that enabled the study of the dependence of both deposition and desorption rates of nerve agents on the indoor concentration.[378,379] The change in the concentration of sarin over time affected by the desorption and adsorption rates of different materials in a building or room was estimated. It was shown, for example, that concrete material without painting has a high deposition rate and low equilibrium concentration, which means that desorption does not occur until the indoor concentration is low. Thus, *unpainted* concrete is perhaps the best general protection material against sarin. The deposition rate onto glass is low, and the desorption rate of sarin from glass is high. Humidity can affect the deposition rate as well as decomposition on glass.[380] No deposition of sarin was observed on alkyd or acrylate paints or on plastic carpet. This can be rationalized by the low porosity of these materials.[378,379] Using concentration profiles versus time, a hypothetical scenario of indoor release of sarin was developed.[377] A sorption model involving sorption rate parameters was also determined for nerve agent simulants such as dimethyl methylphosphonate (DMMP), diethyl ethylphosphonate (DEEP), and triethyl phosphate (TEP).[381]

6.2. Concrete and Construction Surfaces

Several studies of the degradation of nerve agents on naturally occurring surfaces were performed. The degradation pathway of VX on concrete and a detection of its products and relevant kinetic rate constants were investigated.[382] The results showed that VX decomposes on concrete in the same way as in alkaline solution hydrolysis. The reaction product distribution and reaction rate are temperature dependent; the rate increases with increasing temperature (rate doubling approximately every 10 °C). At ambient conditions (24 °C), VX decomposes to 1% of its initial concentration within 9−33 h, and to 1 part in 10^6 within 26−100 h, depending on the basicity of the concrete.[383] Crushed concrete was used here which is more basic than intact concrete. Whereas G. S. Groenewold reported a submonolayer level of VX coverage, Wagner investigated drop-size effects on rate of decomposition.[384] The larger droplets (4 and 2 μL) react considerably more slowly than 1, 0.5, and 0.2 μL droplets. It was also shown that the decomposition rate is higher for "fresh" concrete than for older material, which is explained by the greater basicity for "fresh" concrete.[384] Neither Groenewold nor Wagner observed the formation of EA 2192 (Scheme 2) from basic hydrolysis; but this may be due to the methods applied and limits of detection. VX on other matrices was explored. Decay of VX on the outer surface of asphalt (from local load) has an exponential character ($t_{1/2}$ = 14 days). The formation of degradation product bis-diisopropylaminoethyl-disulfide ($(^iPr)_2NCH_2CH_2S-SCH_2CH_2N(^iPr)_2$) in the outer layer and inner portion of asphalt was observed.[385] VX adsorption isotherms on minerals goethite (common iron mineral in soil; FeO(OH)) and montmorillonite (a clay mineral) and activated charcoal have been obtained.[386] As expected, the greatest affinity of VX was observed for activated charcoal. Montmorillonite has a moderate affinity, while goethite has little affinity. Also, a surface reaction of VX with wet and dry goethite has been investigated. VX was applied in methylene chloride solution (VX purity

>99%) on wet and dry goethite and extracted into water after ~1 d. Recovery from dry goethite was 0%; >90% of the degradation product EMPA was extracted. Wet goethite gives values of 60% and 30%, respectively. Previously, goethite was demonstrated to catalyze the hydrolysis of organophosphorus pesticides such as demeton S, diazinon, disulfoton, and thiometon.[387] It was suggested that adsorption onto specific goethite binding sites can reduce the electron density on phosphorus and enhance nucleophilic attack. Measuring the permeation of nerve agents through construction materials is critical for a greater understanding and to advance the stockpile disposal program. Data characterizing the permeation of the nerve agent simulants DMMP and DIMP through wood, gypsum wall board, cinder block, and brick were obtained.[388] These simulants permeated through wood in a lateral direction, following the wood grain. DIMP penetrates more rapidly (7−20 h) than DMMP (30−120 h). Both simulants permeated the lateral space of brick within 1 h. Concentration−temperature plots for simulants penetrating through gypsum wall board was also presented, showing that the permeation time is generally a factor of 2−4 less at ~32 °C compared with times obtained at RT.

Hydrolysis is the primary degradative pathway for many nerve agents in an aqueous environment (Scheme 1). The degradation of soman and sarin under environmental conditions gives only a few relatively nontoxic products, such as IMPA, pinacolyl methylphosphonic acid, and MPA. The rate of hydrolysis is temperature dependent. At 20 °C and neutral pH, the estimated half-life ranges from 461 h to 46 h for sarin. At 25 °C, in the same environment, the half-lives ranged from 237 to 24 h for sarin and 60 h for soman.[17] VX is more persistent in the environment than G agents: it does not evaporate readily and is essentially nonvolatile from water. Hydrolysis of VX gives many degradation products, depending on temperature and pH. The most dangerous, and thus environmentally significant, is *S*-(2-diisopropylaminoethyl) methylphosphonothioic acid (EA-2192), which is stable under neutral conditions (see above). The rate of hydrolysis is accelerated in the presence of ions. For example, cations such as Ca^{2+} and Mn^{2+} in seawater catalyze the hydrolysis.[389] The half-life of tabun in seawater is shorter (4.5 h) than that in fresh water (9 h).[17] In river water, the hydrolysis rate was enhanced by a factor of 2−4.[390] There is obvious concern about the fate of the nerve agent material involved in past disposal at sea.[391,392] The environmental threats of the sea-dumped chemical warfare material depends on munition type as well as environmental conditions.[98] The Baltic Sea was a site of much dumping,[393] as well as adjacent areas such as Skagerrak and the Norwegian trench.

The fate of nerve agents and their degradation products in soil have recently been reviewed by Munro et al. and Kingery.[17,390,394] In many cases, persistence depends on weather conditions and moisture. More than 90% of sarin is decomposed in soil within 5 days. At low temperature, persistence is increased, and sarin can remain on snow during 2−4 weeks when deposited as droplets. Liquid tabun is stable within 1−2 days under average weather conditions and 2 weeks on natural snow; full NA degradation occurs after 4 weeks. Under a neutral environment, tabun degrades to *O*-ethyl *N*,*N*-dimethylamidophosphoric acid and HCN.[257] *O*-ethyl *N*,*N*-dimethylamidophosphoric acid can further undergo hydrolysis to phosphoric acid, but this ultimate reaction is much slower. In soil, apart from hydrolysis, tabun is subject to biodegradation, nitrile hydrolysis, and *N*-dealkylation. About 16 compounds were isolated from soil contaminated with tabun, but most of them were present at less than 1%.[395,396] Soil studies with VX indicate that 90% of the agent decomposes within 15 days. However, Bellier et al. recovered VX from soil contaminated three months before.[397]

6.3. Landfills

Landfills have been another long-term consideration. Mathematical models were developed for evaluating the suitability of landfills for disposal of contaminated debris and the fate of chemical warfare agents in landfills.[398,399] The fate of nerve agents was evaluated with MOCLA (model for organic chemicals in landfills) with results showing that over 90% of NAs are distributed and remain in the solid fraction associated with the aqueous fraction. This can be explained by a small amount of water present in landfills. The primary fate was hydrolysis. Sarin was completely destroyed within 6 months, whereas soman and VX decomposed much later (>5 years). Since some degradation products are toxic and more persistent in the environment, analytical evaluation of the fate of degradation products is needed.

7. SENSING AND DETECTION

Almost all instrumental techniques that currently unambiguously determine the presence of nerve agents are expensive and nonportable such as gas chromatography, mass spectrometry, and NMR spectroscopy. In an effort to investigate new methods of more selective and cheaper sensing technologies, as well as to monitor safe, affordable, mild, and nontoxic disposal, it is in part essential to better understand transition metal−nerve agent binding and reactivity. Here, we can consider NAs as *ligands*. Because of the complicated behavior of VX in aqueous media (*vide supra*) (Figure 9), there is a need to examine particular interactions and propose distinct model systems to investigate decontamination pathways. Through ligand design, we can effect selective phosphine oxide-type complexation.[400,401] Also, the study of *reversible* agent−metal binding allows for insights into sensor applications. The study of agent−metal interactions is ultimately crucial in understanding how exactly metalloenzymes effect toxic organophosphate/organophosphonate substrate decomposition. Also, simple sodium thermionic detectors for sensing phosphorus compounds are commercially available.[402] Later, colorimetric systems and other methods can be introduced.

7.1. Possible Metal Ion Binding Modes in Solution

In this section, we will deal with reports and insights mainly into *non-bond-rupturing* agent binding in solution to single metal ion systems. There are a variety of binding modes due to the various donor atoms present. We will first cover solution studies in which $[P{=}O\cdots M^{n+}]$ binding occurs. The primary metal (ion) contact is likely through the phosphoryl oxygen in a Lewis base (*L*-type) ligation.[375] X-ray and IR spectroscopic data allow for a better molecular understanding. Interestingly, there is no crystallographic report of a real NA species bound in a metal complex; there is instead a great reliance on model agents such as DMMP. Also the simple consideration of a hydrogen ion (H^+) as a model for a chelated metal species is useful. With any given agent, there are various interactions whose strength will depend on the metal, and the noninvolved ligand. Monodentate interactions with other possible donor atoms will give weaker interactions. The binding of neutral Lewis donor phosphoryl group molecules is competitive with ostensible or adventitious water or with common interferents (e.g., NO_2). Unfortunately, even

moderate humidity might greatly "outweigh" the O═P concentration.

7.1.1. Early Reports of Phosph(on)ate [R_3P═O···M^{n+}] Interactions (R= Alkyl, Alkoxyl). Next, we will discuss early solution and structural studies of O═PR_3, O═$P(OR)_3$, or O═$PR(OR)_2$ M−O interactions with metal ions. To the best of our knowledge, results by F. A. Cotton on a series of phosphine oxide type complexes, involving early reports of O═$P(R)_3$ M^{n+} binding, were not considered in the nerve agent context and have not been reviewed before from this angle. J. C. Sheldon and co-workers reported complexes of the formulation [Br_3P═O···$SnBr_4$], and [Cl_3P═O···$SnCl_4$].[403] Here [Ar_3P═O···M] species were prepared to demonstrate that the [X_3P═O···SnX_4] systems *do* bind through the oxygen. Next, Ni^{2+} complexes with $OPPh_3$ were reported.[401] Ph_3As═O metal complexes were also reported.[404] For a useful list of P−O stretching frequencies, the reader is referred to the Cotton reference.[401] Next, there was a brief review describing the effect metal ion binding has on the P−O stretching frequency.[405] Additionally reported were Co(II), Ni(II), and Cu(II) complexes, with the formulation $(Ph_3P$═$O)M(NO_3)_2$, in which the NO_3^- is bound through one oxygen. In particular, phosphine oxide complexes with Cu^{2+} as well as arsine analogs were studied.[406] The characterization of these molecules was as follows: [$Cu(Ph_3P$═$O)_2Cl_2$], yellow, $\nu_{(P=O)}$ = 1142 cm^{-1}; [$Cu(Ph_3P$═$O)_2Br_2$], dark red, $\nu_{(P=O)}$ = 1145, 1169 cm^{-1}. For free Ph_3P═O, $\nu_{(P=O)}$ is 1195 cm^{-1}. These compounds were found to be tetrahedral. The cation moiety $Cu(Me_3PO)_4^{2+}$ was square planar. Arsenic analogs were yellow-brown ($\nu_{(P=O)}$ = 840 cm^{-1}) and olive green ($\nu_{(P=O)}$ = 842 cm^{-1}). Perchlorate species were also obtained, but the Cl−O streteching bands in the IR spectrum obscured the P═O stretches. In 1966, K. D. Berlin et al. treated MgI_2 with diphenyl phosphinates; it was found that the PO−C bond, not the P−OC bond, was cleaved.[407] This relates to the metal-assisted discussion above. More contemporary M−O−P reports come from F. Gabbai and co-workers, in which DMMP (dimethyl methylphosphonate) was added to 1,2-bis(chloromercurio)tetrafluorobenzene;[408] the ^{199}Hg chemical shift could be monitored, *vide infra*. A crystal structure of the bis-adduct was obtained (Figure 16). The binding constant for this interaction was measured as 3.7 ± 0.4 M^{-1}. There are many crystallographic complexes of simpler phosphonates (*vide infra*). The synthesis and crystal structure of transition metal alkoxides $Ti(OMe)_4$ and $Nb(OMe)_5$ containing organophosphonate ligands $[Bu_4^nN]_2[PhPO_3H]$ were reported.[409] The bridging geometry of phenylphosphonates and IR spectrum band for P═O bond were observed. The simple complexes of related phosphates continue to provide information on complex color and IR signature.

The binding of VX species allows for various monodentate modes but also bidentate modes as illustrated in Figure 17. This was studied by Y. S. Lee and D. G. Churchill, and the binding energies (gas-phase calculations) were provided.[410] In simple metal salt systems, VX and R-VX should possess nearly the same binding, judging from the fact that the steric differences do not come into play at a single metal ion.

The phosphonate diacids are also treated (Figure 18). By their nature, like carbonic acids, they are bound through their deprotonated oxide. A review by J.-G. Mao discusses lanthanides and phosphonates.[411] The variety of phosphonates that are free-standing or connected to other phosphonates are considered in terms of solid state and luminescence. The solid state and luminescence aspects also give "food for thought", important in terms of decontamination or sensing. There is special interest associated with the stability and low solubility of these species.

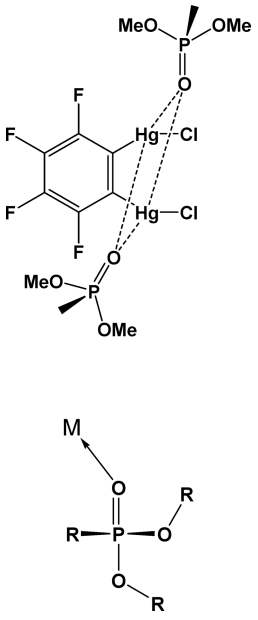


Figure 16. (top) The Hg_2 complex from ref 408 and (bottom) simple phosphoryl binding mode with a single metal ion. The phosphoryl stretch can be conveniently monitored.

There are reports on molecular mechanics calculations, in which organophosphate species bind to lanthanides and become complexes formulated as ML_2.[412] This work is interesting, in that it deals with the reverse situation in which O═P's sequester metal ions selectively. It also ties in with H_2O/P═O phosphoryl metal complexation competition and considers the lanthanide hydration sphere and how bound waters can be displaced by P═O groups.

Also, intermolecular hydrogen bonding study between organophosphorus compounds and phenol, methanol, α-naphthol, and pentachlorophenol are done by T. Gramstad.[413−415] They measure hydrogen bonding association constants. It turns out that enthalpy, entropy, and association constants have a linear relationship with hydrogen bonding frequency shifts.

7.1.2. Coordination Chemistry of Downstream Non-P-Containing Products of Decomposition. Another very important aspect to consider in terms of catalysis is how the decomposition products (Scheme 1) or the downstream components will interact with metal ions. The neutral thiocholine substrate ($HSCH_2CH_2N(R)_2$) (Figure 19) is probably the most recognizable non-P-containing nerve agent degradation product, an essential product of VX hydrolysis decontamination, and a notably strong player in metal chelation because of its simple bidentate design. It offers a stable five-membered metalloheterocyclic interaction with a variety of metals regardless of the R groups (Figure 19). For completeness, we can consider a variety of R groups (e.g., R = Me, Et, but not H). Previously the dimethyl derivative was prepared by J. H. Yoe and by Burke,[416] but no crystal structures were reported. Also Jain studied complexes of diethylamino-ethanethiol with Cr(III), Co(III), and Ni(II).[417] Dimethylaminothiols were also reported with Zn, as in Zn-[$SCH_2CH_2N(CH_3)_2]_2$, which was prepared from the disulfide $(CH_3)_2NCH_2CH_2SSCH_2CH_2N(CH_3)_2$.[418] N,S (diethyl)-type ligands with Al and Ga [$SCH_2CH_2N(CH_2CH_3)_2$] were reported

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

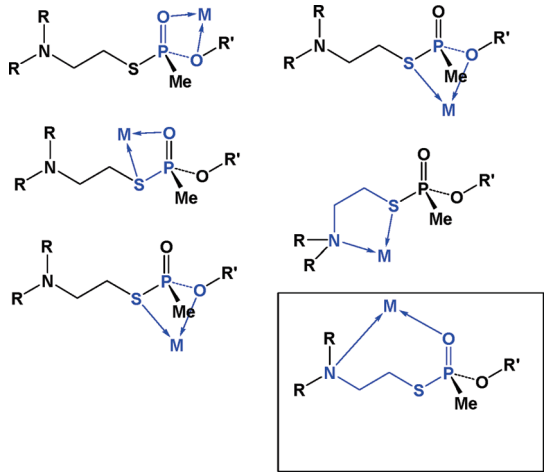


Figure 17. Theoretical binding modes at one metal ion of VX or R-VX. One enantiomer is shown only.

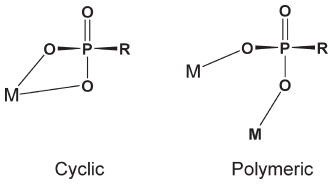


Figure 18. Diagram of non-neutral phosphonate systems.[411]

by C. Jones.[419] The report by G. G. Briand[420] describes the $[SCH_2CH_2N(CH_3)_2]$ ligand with bismuth. There is actually a variation for this ligand coordination in which the sulfur can bind alone. This is also true in the C. N. McMahon report in which Al^{3+} complexes with $[SCH_2CH_2N(CH_3)_2]$ were studied.[421] The $[SCH_2CH_2N(CH_2CH_3)_2]$ ligands with Re[422] and oxotechnetium species have also been described.[423] Diethylaminoethanethiol (DEAT) was studied by Jain,[424] who describes the coordination of 2-dimethylaminoethylthiolate ligands. Na_2PdCl_4 was used as a starting material to give a trimer, $[PdCl(SCH_2CH_2NMe_2)]_3$; the Pt equivalent was made as well. The mono and bis species of $PdCl(SCH_2CH_2NMe_2)(PPh_3)$ were also isolated. Mass spectral as well as ^{31}P NMR spectroscopic data was provided (*vide infra*). Given that $HSCH_2CH_2N(CH_3)_2$ and $HSCH_2CH_2N(CH_2CH_3)_2$ are commercially available; simpler derivatizations can be made.

Mikuriya (1980) studied fragments that have an O-group. These interesting neutral [NSO] fragments were examined with Cu(II).[425−427] These species are also known as v-mercaptamines−aminoethanethiolate and are illustrated as their complexes in Figure 19. Interest in these species is structural only: connected to the aminothiolate is a proximal oxygen ligating atom. Arguably, this is as close as we can get to a stable VX-type structural mimic in which these species bear a dimethylene fragment $[CH_2CH_2]$ in place of a P^{5+} fragment [−P═O(OR)].

There are other decontamination products such as fluoride (F^-) in the case of sarin, soman, and cyclosarin and cyanide (−CN) in the case of tabun. These ions are not unique to nerve agent systems, but their detection is relevant here. There are various fluoride sensing reports. Other substrates such as alkoxides (e.g., EtO^-) and amines ($HNMe_2$) are far too common in our surroundings to be signatures of nerve agent species.

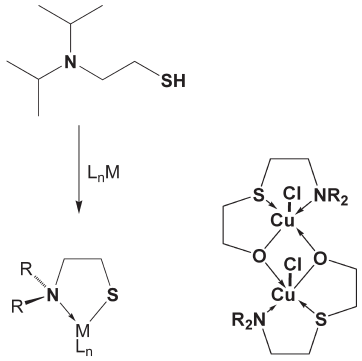


Figure 19. (left) The binding of the thiocholine $(SCH_2CH_2N(^iPr)_2)$ residue to one metal center (R = Me, Et) and (right) stucture of Cu^{2+} aminoethanethiolate species.

Next, the consideration of tabun M^{n+}−N-binding has led us to include one more structural example, which involves a [M←NC−P] motif. This occurs in the example of Na^+ binding of the $[NC-P(CN)]^-$ ion, in which the Na^+ is hosted by an 18-crown-6 ligand.[428] The degree of crystallographic disorder obscured the Na···N bonding distances. Thus, there is still no adequate structural mimic for tabun for a binding mode that is, in light of the great number of known M−NC− motifs, very likely to exist. Also, a mimic of tabun was tested electrochemically based on the β-oxide formation reaction.[429]

7.2. Colorimetric Detection

There are a variety of chemical systems that involve selective color changes as an indication of the presence of an agent or degradation product. There are pertinent older reports such as the amine-peroxide indication reaction or cleavage of indophenyl acetate.[430] Contemporary systems are often metal- or organic dye-containing. One clever scheme involves gold nanoparticle growth catalyzed by the thiocholine produced from AChE degradation of paraoxon, in which nanoparticle growth is then inhibited by the thiol.[431] The increase in nanoparticle size gives a change in color. Another report utilizes a tetraphenyl-porphyrin (sulfate) in a displacement assay, as tested with diazinon, malathion, paraoxon, and coumaphos.[432] On this sensor surface, AChE systems are anchored and their active sites are occupied by the porphyrin, which is then displaced by an agent. The released porphyrin gives rise to an optical signal (decrease of 412 nm band when released; limit of detection 7 ppt). Also, there is a report involving molecularly imprinted polymer (styrene and diacrylate, combined with a nerve agent mimic).[433] There is a report by A. M. Costero et al. that describes the use of a diaza species with a tethered alcohol; this undergoes color changes upon interaction with $(EtO)_2P═O(Cl)$, $(^iPrO)_2P═O(F)$ and $(EtO)_2P═O(F)$.[434] Later, A. M. Costero utilized azo and stilbene derivatives for detection of DCP, DFP, and DECP.[435] For optical detection of fluoride ion after hydrolysis of DFP, a polymeric membrane containing Al(III) octaethyl porphyrin and ETH 7075 chromoionophore was developed.[436] Changes in absorbance occured due to the deprotonated form of chromoionophore. Indicator pH paper also can be used as a detector if enzymatic hydrolysis of acetylcholine by acetylcholinesterase into acetic acid and choline is taken into account.[437] The presence of organophosphonate inhibits acetylcholinesterase, and hence, no change of pH is observed. Inhibition of acetylcholinesterase activity also was used in paper by D. S. Prokofieva for

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

spectroscopic detection of soman.[438] Silicon nanoparticles functionalized by thiol groups and aliphatic alcohols were prepared for chromogenic detection of nerve agent mimics.[439] Squaraine dye was used to produce a chromofluorogenic response.

7.3. Chemiluminescence: Fluorescence and Phosphorescence

There are various systems that instead of, or in addition to, giving clear colorimetric signals, give clear fluorescent signals. Some agent derivatives are naturally fluorescent due to their substitution or derivatization and thus can be monitored by UV−vis. The catalysts can be lanthanide-based such as those by Murray and Jenkins and co-workers[440,441] or organometallic as reported by L. Y. Kuo et al.[161]

7.3.1. Lanthanide-Based Catalysts. Regarding f-element systems, inherent and fingerprint luminescent properties of the lanthanide ions (f−f orbital electronic transition) upon, for example, phosphonate binding is in theory possible. Murray reports devices involving Eu^{3+} serving as the basis for sensing of the phosphonic acid degradation product of sarin and soman in a copolymer.[441] This representative report by Murray involves PMP (pinacolyl methyl phosphonate) and establishes a half-life index. Lanthanide ions, especially those in aqueous environments, may have variable coordination numbers (8, 9, and higher). In this context, Eu^{3+} with a coordination number of 9 was established; $Eu(DMMB)_3(PMP)(NO_3)_2$ optical responses with PMP $Eu(DMMB)_3(NO_3)_3$ gave rise to an optical band at ∼610 nm; $Eu(PMP)_3$ gives a peak at 613 nm; DMMB = 3,5-methyl dimethylbenzoate was also used. The limit of detection in this work was reported at ∼125 ppt. In the resulting (4−5 mol %) polymers, the 610 nm signal is weak. Results from a 3 mol % polymer loading possessed the best features. The complex percentage was kept low to allow for less cross-linking, making it easier for liberation of adsorbed PMP.

7.3.2. Organometallic-Based Sensors. There are some notable organometallic-based sensors. One involves a BODIPY system: a boron dyad that is a CN^- sensor (intended for tabun).[442] An organometallic approach also comes from a report in *Angewandte Chemie, International Edition*.[443] There are also ferrocene-based systems discussed later in the context of electrochemistry (*vide infra*).[444]

7.3.3. Organic Design. Some sensors are simply fluorogenic organic compounds.[445,446] The A. J. Rebek et al. report underscores how a research group with the reputation of creating elegant host−guest designs approaches nerve agent detection and degradation chemistry (Figure 20).[447] In the molecular system shown prior to nucleophilic attack, the tertiary amino lone pair of the probe is engaged electronically via photoinduced electron transfer (PET) with the delocalized pyrenyl system. Upon addition of DCP, this lone pair achieves intramolecular ring closure and removes the PET quenching mechanism pathway allowing for natural pyrenyl fluorescence. Further, there is a theoretical study that stems from this report as well.[448] S. Han published application of rhodamine−hydroxamate rearrangement in the detection of nerve agent simulant DCP.[449] BES-Thio fluorescent probe based on fluorescein can be used for the direct detection of neve agents possessing a thiocholine leaving group.[450] A. Akthakul et al. developed a sensor containing the Nile Red dye.[451] The device demonstrates over an order of magnitude increase in vapor sensitivity for the sarin simulant DMMP when inorganic oxides were used as a quencher. An organogel containing a 2-(2′-hydroxyphenyl)benzoxazole group

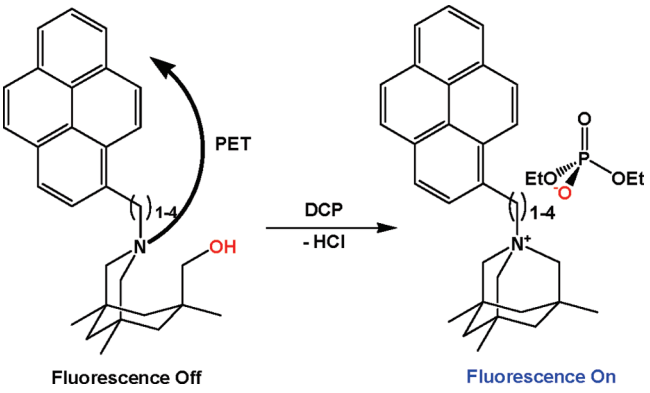


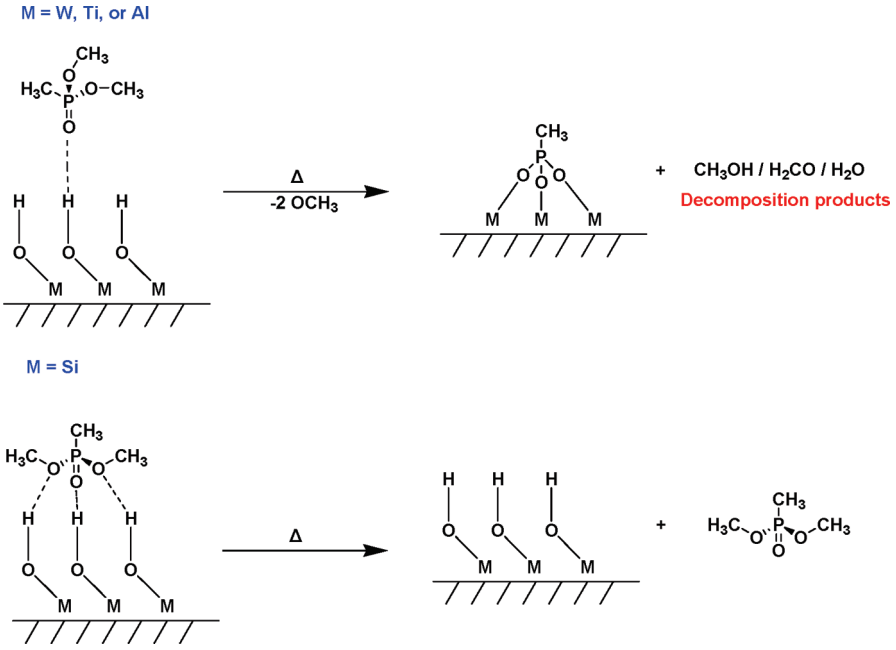
Figure 20. The Rebek group system.[447]

was synthesized and tested for detection of nerve agent simulant.[452]

7.3.4. Biologically-Based Luminescence Detection. There are various detection designs stemming from strictly *biological* systems. Uses of green fluorescent protein (GFP) in this context have been reviewed[453−455] with a pair of reports coming from Wu[454,455] and a notable example involving paraoxon in 2002.[454,455] In terms of GFP technology, paraoxon was also studied with a yeast biosensor.[456] Next, terbium was employed as a luminescent probe in attempting to learn whether tryptophan is close to the Ca^{2+} binding site in human paraoxonase.[457] Biosensors that are fluorescent have been developed.[458] Next, the phnD protein product of *E. coli* was studied with the natural $(HO)_2P{=}O(CH_2CH_2NH_2)$ derivative; changes in fluorescence with binding to $(HO)_2P{=}O(Me)$ were absent.[459] Organophosphate hydrolase (OPH) mounted on silica gel was prepared to determine $(^iPrO)_2P{=}O(Me)$.[460] A fiber-optic OPH biosensor was developed.[461] This device is extremely selective to organophosphates such as parathion, paraoxon, and coumaphos. Also it can be applied to the measurement of different organophosphorus esters in a mixture. Organophosphorus acid anhydrolase (OPAA) was studied with fluorine-containing species.[462] There has been a report by Briseno-Roa involving species with fluorescent leaving groups that allow for the screening of potentially active hydrolytic enzymes.[263] Paraoxon, parathion, dimefox, DFP, tabun, sarin, cyclosarin, soman, VX, and Russian-VX were conjugated with the optically reporting group 3-chloro-7-oxy-4-methylcoumarin. This moiety gives rise to fluorescence upon P−O scission that can be monitored by emission spectroscopy. Laser-induced fluorescence (LIF) was used[463] in which eosin was the indirect LIF (electrophoretic) dye for EMPA, MPA, and VX. A limit of detection of 30 μM (VX) and 37 μM (EMPA) was reported. The instrumental aspects of micro-X-ray fluorescence (MXRF) were discussed in which a peptide library was utilized.[464] Also, the fluorescence and CD properties of OPAA (E.C.3.1.8.2) were monitored with $(^iPrO)_2P{=}O(F)$.[465] Separately, there were two FRET-based methods used in the detection of methylphosphonic acid.[466] A DNA aptamer sequence was bound covalently via tosyl groups onto magnetic beads.

7.3.5. Polymer and Bead Supports. A polyhedral oligosilsesquioxane nanosensor was reported that details remote sensing capabilities.[467] Also microspheres (1−10 μM) were used for PMP detection involving molecularly imprinted polymers.[468] The polymeric medium involved methacrylic acid and divinylbenzene. Next, a report describing carboxylate-functionalized microbeads that give a

Scheme 32. Absorption and Desorption of DMMP on Various Metal Oxide Surfaces



"turn-on" optical response upon treatment with $(EtO)_2P{=}O(Cl)$ has been made.[469] The amine group of fluoresceinamine, which is adsorbed by poly(2-vinylpyridine)-coated microbeads, undergoes reaction with chlorophosphonate. Here, the HCl is trapped at the nitrogens of the accompanying pyridyl groups. A chemical sensor based on a molecular imprinting technique with a silica matrix was developed and tested on PMP and VX simulants.[470]

7.4. Porous Silicon

Porous materials constitute a useful platform that enables the detection of a wide array of target molecules and materials.[471] Among these materials, porous *silicon* has been of recent interest in nerve agent detection. C. P. Tripp and co-workers studied the binding between organophosphonate and the silica surface with IR spectroscopy.[321,323] Absorption changes in the silica SiO−H stretching mode in the IR spectrum allow for detection of DMMP, TMP, MDCP, and TCP. The signal depends on the hydrogen bonding environment; the energy of the band decreases in this order: TCP < MDCP < DMMP < TMP. The absorption of DMMP on the SiO_2 surface is different from other surfaces such as WO_3, TiO_2, and Al_2O_3. In the latter cases, binding of DMMP with the metal oxide surface occurs through H-bonding at the P═O group, and at elevated temperatures, stable methyl phosphate groups remain attached to the surface, while methoxy groups are eliminated.[324,472,473] In contrast, silica surface binding occurs at the oxygen atoms of methoxy groups through H-bonding and, at elevated temperature, leads to desorption without decomposition of DMMP (Scheme 32).[304]

Porous silicon made by electrical etching can detect HF gas produced by hydrolysis of fluorophosphonate esters (e.g., sarin, soman, GF, and DFP).[474,475] A TMEDA[Cu(II)] (TMEDA = tetramethylethylenediamine) complex[476] acts as a catalyst for the hydrolysis of DFP and accelerates production of HF gas (Scheme 33).[477] Also, the addition of surfactant enhances HF gas production; HF acting on the porous silicon oxide interferometer gives rise to a changed response to SiF_4 gas resulting in a blue (hypsochromic) shift (∼15 nm) and an intensity decrease in the Fabry−Pérot interference fringe.[474]

A distributed Bragg reflector (DBR) porous silicon interferometer allows for the detection of DMMP, TEP, and DEEP. Exposure of this device to a simulant results in a red (bathochromic)-shift of the DBR reflection peaks.[342] The first (22 nm) and second DPR peaks (32 nm) undergo red-shifting as seen for DMMP detection. The two reflection band systems show more red-shifting than the one reflection band system.

7.5. Carbon Nanotubes

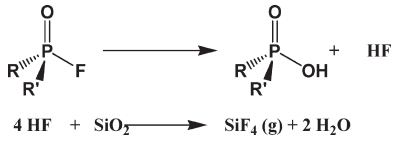
Carbon nanotubes are a naturally good material choice for sensors due to their nanoscale diameter and electrical and electrochemical properties. Carbon nanotubes decorated with nickel nanoparticles were used for electrochemical detection of 2-diethylaminoethanethiol, degradation product of the V-type nerve agent.[478] Pd-contacting single-walled carbon nanotubes (SWNTs) and Au-contacting SWNTs were tested by Y. Kim et al. to detect DMMP gas.[479] Pd-contacting SWNTs exhibited detection levels as low as 1 ppm. DMMP vapor in concentrations below 1 ppm also was detected with SWNT thin films integrated with polyimide substrate.[480] Some theoretical calculations of interaction of nerve agents with SWNTs were also performed.[481] Ferrocene−amino acid conjugates noncovalently bonded to multiwalled carbon nanotubes (MWNTs) on indium tin oxide surfaces also change their electrical properties after reacting with mimics for tabun and its degradation products.[482] Later, P. M. Diakowski et al. prepared MWNTs covalently modified with ferrocene−lysine conjugate.[483] In this case, detection of nerve agent simulant occurred at micromolar level. Hexafluoroisopropanolphenyl derivatives were used for functionalizing SWNTs, and sensors can detect DMMP with a detection limit below 50 ppb.[484,485]

7.6. Extraction and Analysis

7.6.1. Overview: Checking Compliance Techniques Used in General. Many techniques are used for the extraction

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

Scheme 33. Hydrolysis of Fluorophosphonate Esters and Removal of HF Gas by Silicon Oxide[a]



[a] From ref 474.

of nerve agents from aqueous environments. Extraction and analysis of nerve agents and their degradation products have been previously reviewed by R. M. Black and B. Muir in 2003.[486] This review summarizes GC and LC analysis of NA reagents. In 2008, H. Thiermann and co-workers reported LC-MS-based nerve agent analysis.[3] Here, we will cover other methods and recent reports about extraction and analysis. Extraction by various methods, followed by analysis with chromatographic tools (GC, LC, and HPLC), has been used previously for nerve agent separation. In the liquid phase, ion-pair liquid−liquid−liquid microextraction of MPA, EMPA, IMPA, and CMPA is done with 1-octanol solvent and the assistance of tri-*n*-butyl amine ion-pair complexes.[487] Ion-exchange solid-phase extraction (SPE) methods using strong cation-exchange[488] and anion-exchange[489−491] cartridges are reported. Molecular imprinted solid phase extraction,[492,493] using methacrylic acid (MAA) and pinacolyl methylphosphonic acid (PMPA), and solid phase-extraction followed by analysis with HPLC with ^{13}C-isotope column technique[494−496] were also reported. Lastly, solid-phase microextraction (SPME), combined with an ATR−FT-IR spectrometer,[497] LC-ESI-MS/MS, DESI-MS/MS,[498] and GC/MS[499,500] analysis were developed and used for extraction and analysis of nerve agents.

Recently, a new microextraction technique, HF-LPME (hollow fiber liquid-phase microextraction), was developed by H. K. Lee and was used for extraction of triazine herbicides.[501] V. Tak et al. reported that the HF-LPME method is efficient for extraction of nerve agent mimics and real agents such as DIMP, DEDEPA, DCHMP, DEPS, sarin, CMPF (cyclosarin), EDEPC, and SM from water.[502] There are many extraction parameters, and extraction is performed under optimized conditions: a polypropylene hollow fiber, using trichloroethylene (1 μL) as extraction solvent, 1000 rpm stirring speed, 15 min extraction time, and 30% NaCl aqueous solution. Extracted compounds were analyzed by GC-MS spectrometry. The detection limit of these systems is 0.1−10 μg/L, which is better than a nonsalt water system (detection limit 0.5−200 μg/L). Also, the HF-LPME method is used for detection of degradation products of chemical warfare agents[503−505] and alkylphosphonates at the concentration of 0.5−0.75 μg/mL from water.[506]

7.6.2. Soils. Extraction experiments of VX from natural soils were performed by B. Bellier et al. in France.[397] The authors analyzed two kinds of soils: local soil (neutral silt loam) and tropical soil (acidic sandy silt loam, French Guyana). A VX dichloromethane solution was used to treat each soil ("spiking" level < 10 μg/g); then, the mixture was allowed to homogenize (3 months). The soils containing VX were mixed with tris buffer (pH 9); extraction with dichloromethane/hexane (v/v 85:15) gave the best recovery numbers. Importantly the pH of the soil buffer solution should be quite close to the pK_a value of VX and quite low to avoid basic hydrolysis. Other reports as well describe the extraction of nerve agents from soils with spiking levels of 0.1−10 mg/g,[390] 0.4% extraction with dichloromethane,[507] spiking level of 0.5 mg/g with 8% ± 6% of recovery,[508] and a spiking level of 20 μg/g with 16.2% ± 1.3% of recovery.[509] A hexane−benzene mixture was used for extraction of sarin from soils; and gas-chromatographic separation and flame ionization detector helped in the analysis of a trace amount of nerve agent at a level of 10^{-4} mg/kg.[510] Concentrations of VX and sarin in slag also can be determined by derivatization of them with optically active alcohols.[511] Also, the spiking and extraction of nerve agents from asphalt[385,512] and concrete[513] are reported. Detection of nerve agent degradation products in soil using capillary electrophoresis is described by A. Seiman.[514] A patent exists as well on devices for nerve agent extraction through application of an external electrical field.[515]

7.7. Common Spectroscopic Techniques

Almost all current instrumental techniques that unambiguously determine the presence of nerve agents are generally expensive and nonportable, such as gas chromatography and (multinuclear) NMR spectroscopy. There has been a long-standing interest, first among inorganic chemists, about how organophosphonates bind to metals, and next by analytical chemists, about how an adequate detection device can be engineered. Ligand optimization and reporting media continue to be explored in NA detection efforts that involve various spectroscopic techniques such as IR and NMR spectroscopy.

As has been underscored by the inclusion of many spectral absorbances throughout this review, IR spectroscopy is indispensible for many systems mentioned herein; direct access to monitoring the phosphoryl stretch is very useful. Electron-poor ions such as Fe^{3+} and Cu^{2+} favor stronger coordination and give [P═O] stretching frequencies concomitantly lower by 30−100 cm^{-1}. Some other functionalities, such as perchlorate Cl−O stretches, can obscure P═O absorbances. Agents themselves are not significant absorbers or emitters in the UV−vis spectral region,[516] unless they are specifically modified with, e.g., a fluorescent coumarin-type leaving group.[263,517] With the inclusion of a photoabsorber material, such as a porphyrin, we can monitor this conveniently by UV−vis methods.

7.7.1. NMR Spectroscopy. NMR spectroscopy supports many areas of chemistry and science. NMR spectra have found great utility in monitoring reactions and characterizing new compounds and also, for example, in detection of agent and agent remants.[518,519] NMR can be used as a definitive part of determining nerve agent (or remnant) presence. There are numerous nuclei that can be brought to bear in NA studies, especially the ^{31}P nucleus. Analytes that contain characteristic ^{13}C, ^{1}H, and ^{31}P, as well as ^{15}N and ^{19}F, NMR signals can be probed.[520] This of course assumes the absence of paramagnetic ions and the necessary solubility of some species. In terms of assignments of agents in solution, the contribution by Yang and co-workers should also be mentioned,[521] as well as work of Van den Berg et al.[522] Many studies have focused on ^{31}P NMR spectroscopy.[151,314,344,349,408,523,524] Other NMR active nuclei and related experiments also are found in the literature. The types of experiments have involved HSQC NMR,[525−528] as well as magic angle spinning (MAS).[346] Next, shift reagents can change the phosphorus δ value.[32,529] One early study involved mixtures of $(Me_2N)_3P$═O, DMMP, or $(MeO)_3P$═O, in the presence of Be^{2+} and Al^{3+} ionic centers.[530] Next a series of phosphates was treated with Co^{2+} and Fe^{3+}.[531] The species $(MeO)_3P$═O, $(EtO)_3P$═O, and $(MeO)_2P$═O(Me) were all

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

found to give shifts upon binding; also P−H decoupling was observed. With this technique, changes in P−S bonding can be monitored.[532] Variable-temperature ^{31}P NMR spectroscopy was used in studying resin-based systems with two DMMP adsorption sites, the macroreticular region and the quaternary ammonium hydroxide ion-exchange sites.[344] It was found that DMMP may migrate from one site to another.

In this next section, the uses, limitations, and details of NMR spectroscopy are provided. There are techniques that allow for detection of the various stereoisomers of the nerve agents; see Figure 4 in Van den Berg et al.[522] There is also a report of lanthanide-induced shifts from authors who have also been active in the organophosphonate sensor area.[533] An NMR spectroscopic assay was also developed to conveniently determine the purity of live agents.[534] ^{31}P NMR spectroscopy can also be used in studies that involve enzymes that degrade agents.[532,535] Studies that successfully determine discrete cleavage events have used ^{31}P, including the L. Y. Kuo and H. Koskela reports.[161,528] In terms of calculational efforts, ^{1}H, ^{13}C, ^{31}P, and ^{15}N NMR spectroscopic values were simulated (calculated) by I. Bandyopadhyay et al. and compared with actual literature values.[410]

Nuclei other than ^{1}H, ^{31}P, and ^{13}C NMR also occasionally hold prominence. The ^{27}Al, ^{113}Cd, and ^{199}Hg nuclei have been utilized in (i) monitoring adducts or (ii) mineralization. First a study of magic angle spinning in ^{27}Al NMR spectroscopy was utilized.[314] Herein, VX, GB, GD, and HD were allowed to form complexes on the nanosize Al_2O_3 (AP−Al_2O_3) material surface. The ^{29}Si nuclei was used in helping to characterize supports and in monitoring changes in these systems during sensing or decontamination.[536,537] The use of ^{113}Cd NMR spectroscopy was included in a report by Omburo et al.[249] ^{199}Hg NMR spectroscopy has been used by Gabbai and co-workers to characterize a double DMMP adduct; a ^{199}Hg NMR spectroscopic downfield shift helped support the role of direct O−Hg binding of DMMP in solution.[408] In studies in which the aminothiolates are formed, ^{15}N NMR spectroscopy was undertaken,[538] and ^{119}Sn NMR spectroscopy has been previously utilized.[538]

7.8. Related X-ray Diffraction Studies

Single-crystal X-ray diffraction studies help elucidate the intricacies of agent structure and potential binding possibilities that help open up a window for future sensing possibilities. We have conducted particular CSD searches on direct and related (and important) crystallographically known fragments. The [M···O═P] group can be quite well quantified using various species in terms of bond lengths and bond angle. Much is known about [M···O═P] interactions from phosphine oxides, but few structural studies have been performed on groups other than [R_3P═O] moieties (R = alkyl, aryl). From a survey of [(C−O−)$_2$(C−)(P═O····M)] (M = any metal) structures in the *Cambridge Structural Database*, version 1.12 (www.ccdc.cam.ac.uk), the mean P═O bond length in [P═O···M^{n+}] interactions is 1.48 Å and the mean M···O bond length is 2.33 Å (Figure 21).

Next, we can describe what is known about some particular NA-related motifs below. There were ∼60 search "hits" for the (M−O)$_2$P═O(CH$_2$−) fragment (CSD) from reports that include those of Ochocki,[539] S. W. Ng,[540] and R. T. Paine and coworkers.[541] The significance of these structures is that they resemble a deprotonated acid fragment bound through three atoms to one metal center. (CH$_2$)$_2$ could be thought of as holding the place of [−P═OMe(OR)−]. This motif is realistic with respect to a degraded sample in which the (−OR) has been hydrolyzed off.

7.8.1. Protein Structures. Protein X-ray crystallography has come of age and allowed a development of our understanding of AChE, OPH, and related enzymes. Of particular relevance are data that involve the enzyme and phosphorylation events. One study involves AChE in which the effect of enzyme aging is elucidated.[542]

7.9. Electrochemical Sensors and Detection Protocols

Electrochemical methods are simple, versatile, and practical, in terms of controlling and altering the behavior of redox materials. Transition metal ions here have exploitable properties. Such equipment is not too bulky, in theory, to have a portable device, especially in regards to recent lab-on-a-chip research efforts. In recent years, certain reviews in this area deal with biosensing.[15,25,26] Electrochemistry is now strongly linked to biosensing.

As far back as the early 1960s, there was activity in this area and reviews of the literature.[543] Guilbault and co-workers worked on organophosphonate electrochemistry[543] with sarin, (EtO)$_2$(EtSCH$_2$-CH$_2$S)P═O, parathion, and malathion. There were reports of a mercury surface with which polaragram data was recorded. Chemical groups point outward and waters are replaced stepwise in a Cu^{2+}-complex by the surface-active compounds R_3P═O.[544] In the late 1990s, there are notable electrochemistry papers by A. and P. Mulchandani dealing with organophosphorus hydrolase.[545−547] Also, some studies involve the use of phthalocyanines. Thus, this section involves structurally positioned redox-active metal ions that do not directly bind with agent donor atoms. Recently, electronic tongue array, consisting of an eight working electrodes (Au, Pt, Ir, Rh, Cu, Co, Ni, and Ag) was used to detect nerve agent simulants DCP and DECP in aqueous environments.[548] Some common ferrocene-type systems, such as those used in electrochemistry, are described next.

7.9.1. Ferrocene and Phthalocyanine-Based Sensors. There was a report involving an aminoferrocene derivative by N. W. Duffy. (EtO)$_2$P═O(CN) is sensed by an aminoferrocene species [[(BocNH)Fc(CO)CSA]$_2$] bound by a cystamine linkage to a gold substrate. A covalently bound phosphoramide species is produced after the boc group is removed (deprotection) giving a markedly different electrochemical potential.[444] There was also an exploration of $Co^{2+/3+}$ phthalocyanines (redox reaction) in which DMMP was studied using interdigitated electrodes.[549] In this report, thin films (∼50 nm) of phthalocyanines were the subject of electrochemical studies with O_2 as an interferent. The phthalocyanine was either a free-base or the cobalt species on gold electrodes. [The Lewis basicity ($-\Delta H^{\circ}_{BF_3}$) of the analyte scales was 10−135.] Next, SW nanotubes were prepared that were functionalized with tetraaminophthalocyanine cobalt-(II).[550] In this array, electrocatalytic response limits of detection of 8.0 and 3.0 μM were determined for dimethylaminoethanethiol and diethylaminoethanethiol, respectively. The subsequent amount of thiocholine is detected by the electrooxidization from applied current. Co−phthalocyanine thin films (∼50 nm) were also tested with various electrode metals (Pt, Pd, and Au).[551] Voltages were measured when DMMP was used with water, methanol, and toluene in the gas phase. One report by K. A. Sashi dealt with the thiocholine generated from acetylthiocholine when treated with AChE.[552] An enzyme electrode was used for amperometric detection of the thiolate degradation products of demeton-S.[552] DMAET and DEAET were used and were selectively detected at 2.0 and 0.8 μM concentration, respectively.

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

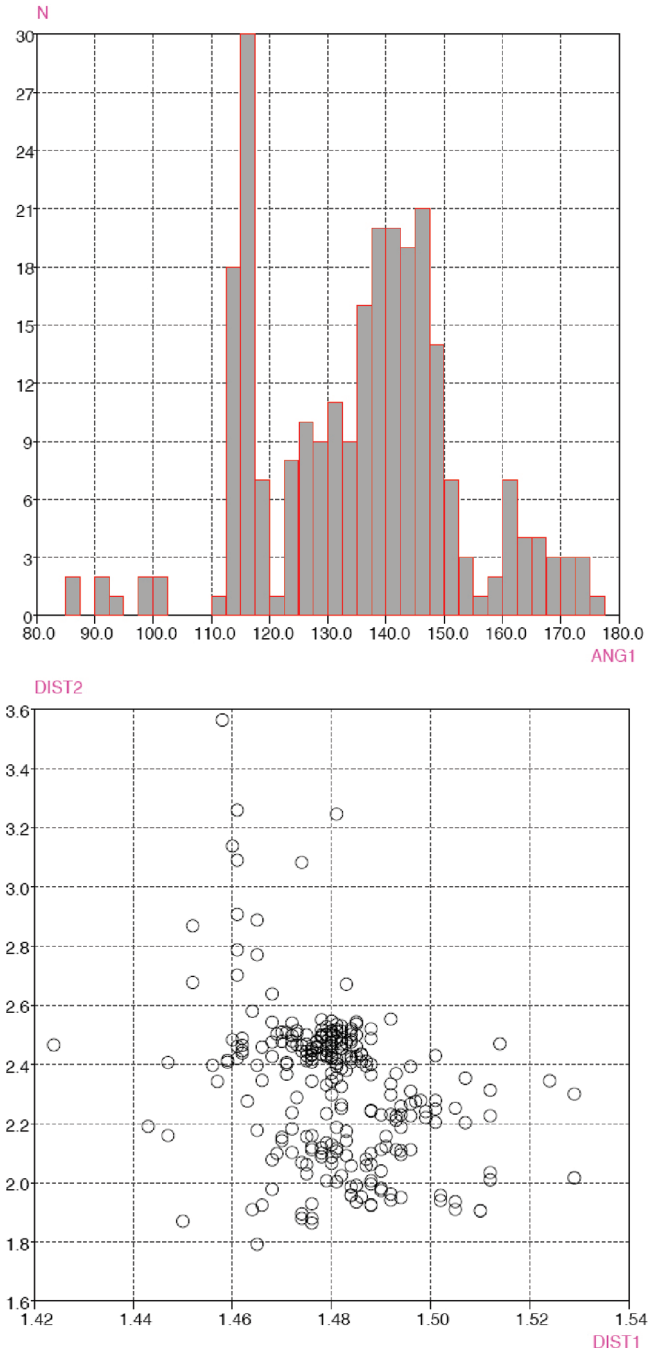


Figure 21. Histograms of (top) [P═O···M^{n+}] angles and (bottom) [O···M^{n+}] (*y*-axis) and [P═O] (*x*-axis) distances.

AChE and carbon nanotube reports were also made.[553] There is a 2008 report that deals with electrochemical detection of VX in blood; it gives a limit of detection of 4.0×10^{-7} M.[554] This is compared with an assay involving Ellman's reagent with a limit of detection of 5.2×10^{-7} M. Ellman's derivative is 5,5′-dithiobis-(2-nitrobenzoic acid) and its transformation to the 2-nitro-5-thiobenzoate anion gives rise to a signature absorption (λ_{max} = 412 nm). Immobilized butyrylacetylcholinesterase on electrodes with Prussian blue ($Fe_7(CN)_{18}(H_2O)_{14-16}$) was involved in detecting residual enzyme activity with sarin (limit of detection = 12 ppb) and VX (limit of detection = 14 ppb).[555] Copper phthalocyanine chemically incorporated in polypyrrole was prepared for sensing of DMMP.[556] Lastly, the impedance of metallic carbon single-walled nanotubes was used in determining a binding model with analytes that include organophosphonates.[557]

There are also studies that focus on the selectivity gained by the F-electrode, of great utility in the detection of hydrolysis components of sarin, cyclosarin, and soman. Xi et al. discussed potentiometric detection of degradation products from ($^{i}PrO)_2P═O(F)$ hydrolysis.[558] The detection limit is lowered with the help of a F^- ion selective electrode (2×10^{-6} M).

Other techniques inherently require electrochemical methods. Electrochemical methods are known for micromechanical systems that are used in testing DMMP.[559] Microchip electrophoresis combined with electrochemistry was also reported.[560,561] Microfluidic separations of alkyl methylphosphonic acids (paraoxon, methylparathion) were reported through the method of contactless conduction detection.[562] The limit of detection for this was 48−86 $\mu g\ L^{-1}$. Another method of electrophoresis using a polymer instead of glass matrix, involved a contactless conductivity detector able to determine both anions and cations at the same time.[563] Also, a detector intended for naval vessels was reported.[564] This ceramic−metal gas sensor utilized cyclic voltammetry; its design was meant to be versatile and robust. Gold nanoparticle immunosensor systems have also been reported.[565] PMP and MPA were detected using techniques that include SPR and potentiometry. Sensing involved an electrochemically cross-linked carbazole/Cu^{2+} dendrimer constituting a SAM sensing platform.[566] The amines interact with the agent and Cu^{2+} ions; whereas the carbazole allows for cross-linking and for a discrete potentiometric response. Next, detection of VX-type degradation products DMAET and DEAET was provided through a polypyrrole sensor combined with PQQ (pyrroloquinoline quinone) (Figure 22) giving respective detection limits of 4.5 and 3.0 μM, respectively.[567]

A small number of reports involve an important part of the chemical detection system or sensing array that was synthesized electrochemically.[568] These kinds of methods were used in preparing a silver substrate.[337] Ca^{2+} experiments are performed with a calcium ion probe with $(CH_2CHCH_2)_2P═OPh$.[569] When substrate Ca^{2+} ion binding chemistry is considered, simple binary compounds such as $CaCO_3$ and can also be considered. The full knowledge of how such metal ions and inexpensive systems are capable of interacting effectively and usefully with the various organophosphonates is important and not fully obtained. Later, some such important basic chemistry issues are touched on (*vide infra*).[570] Separately, there have been studies focused on cellular systems. In 2001, studies on neurons using pinacolyl methylphosphonic acid (PMPA) were conducted to determine its neurophysiological effects in model systems.[571] Some more methodological reports are also mentioned, such as an amperometric study of paraoxon and methyl parathion[572] and a single run approach involving parathion.[573]

7.10. Uses of Mass Spectrometric Techniques

The nature of mass spectrometry (MS) with its requirement for electron beams, resulting fragmentation, and reliance on secondary (tandem) techniques such as gas chromatography for analyte sensing makes MS a special technology for consideration. The general expectation with this rapid screening technique is that the limits of sensitivity can be pushed to extremes, beyond those for other techniques. MS in this area has been the subject of occasional reviews.[28,574,575] Mention in the articles is of particular

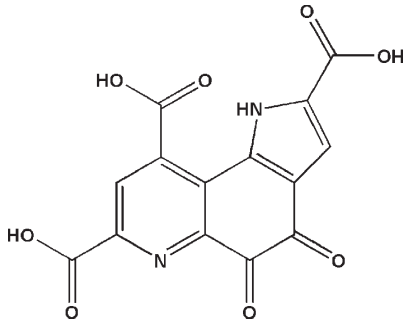


Figure 22. The structure of pyrroloquinoline quinone (PQQ).

agents such as sarin,[83,490,494,495,498,576−590] soman,[490,494,495,498,578,579,582,581,584,588,587,591−595] tabun,[69,70,596,498,579,592] and VX.[382,383,488,490,494,495,499,500,513,597−608] Tandem separation techniques will not be emphasized here. Also, surfaces (e.g., concrete) were considered in their own section (*vide supra*). The types of MS techniques include MALDI-TOF, GC-MS, GC-ICPMS, ESI, SPAMS, and desorption electrospray. MALDI was presented as an effective way of determining widespread emergency events (telemedicine). Also, it is common to silylate the agent or agent degradation products prior to analysis. Here, we will mention key reports and studies that focus on mass spectrometry as a central definitive theme.[609]

7.10.1. Confirmation of Actual Use on Civilians or Conflict Zones. The most pertinent reports invoking the use of mass spectrometry have been the ones that give definitive evidence of actual terrorist or rogue military agent use. First, in the 1988 attack on the Kurdish town of Birjinni, claims that chemical warfare agents were used by the then rogue Iraqi command were verified analytically by GC-MS and GC tandem.[83] Various forensic samples were analyzed; the existence of (^{i}PrO)(HO)P═O(Me) and (HO)$_2$P═O(Me) degradation products was thus supported. Also importantly, *unreacted sarin* was detected. In addition to nerve agents, decomposition products were also detected. Next, Benchop and co-workers reported the *in vivo* detection of nerve agent degradation products from victims of attacks in Tokyo and Matsumodo (Japan);[590] a detection level of 2−135 ng/mL was reported in human beings. The higher values were interesting because of the apparent contamination in some survivors of NA doses above the proposed lethal limit. Next, there was a study involving the serum of a Japanese victim (Osaka area), which contained degradation components of VX.[605] Separately, the Japanese report contains analyses of brain tissue from autopsies of victims.[589] In the serum sample, not only EtO(P═O)MeOH was present, but also (^{i}Pr)$_2$NCH$_2$CH$_2$S(Me) was detected. This was the first evidence of an actual human VX victim and underscores the importance of determining which metabolites are present in serum, and how VX or other agents are metabolized in the human body.

7.10.2. General Reports. The reports of mass spectrometry stemming from ∼1980 mark a steady progression in the art; a growing important conjunction with other methods (chromatographic methods) is also seen. Also, progress toward biotechnology (identifying and targeting biomarkers) is a main advance in this field. A 1979 report deals with detection by MS of species that include (RO)$_2$P═O(R′), (RO)P═O(R′)F, (RO)P═O(R′)(SR″), and (R$_2$N)P═O(OR′)(CN).[610] This study compared electron impact and chemical ionization methods. MS also provides support for some surface-based studies. The detection of DMMP on Pt(111) was supported by MS techniques;[299] it was shown that DMMP was bound to the surface in that it was able to desorb and be detected intact. Also, a Mo(110) surface was monitored for DMMP desorption products using MS.[296] Next, thermospray LC-MS was used to determine VX degradation; 200 pg could be detected of the H$^+$ ion of VX.[606] Herein, spiked river samples were used; the detectable amount from 50 mL was 1 ng/mL. This ionization relates to the recent geometry-optimized calculation of [(OMe)(Me$_2$NCH$_2$CH$_2$S)P═O(Me)][H$^+$] in the gas phase.[410] Ionization processes for soman and tabun were also determined by taking the ratio of photo- and thermionic signals.[592] In 1999, VX was reported as being detected directly using ion trap secondary ion mass spectrometry.[603] The samples involved milligram scale soil samples from which intact [VX + H]$^+$ and fragments were detected (0.4 monolayer coverage). These experiments were also supported by calculations of protonation of the tertiary amino nitrogen.[410] Here, deuteration was also conducted to show that the C$_2$H$_4$N(^{i}Pr)$_2^+$ fragment allows for NH proton transfer to the phosphonothioate (RO)P═O(R′)(SR″). This occurs in concert with or before the C−S bond cleavage event. In a 2000 report, liquid samples were analyzed by HR electrospray ion mobility methods.[611] Here, phosphonic acids in the negative mode were determined in the ppb range. As metioned in the ^{31}P NMR context, the degradation of DMMP was determined in 1995.[608] Next, electrospray ionization ambient pressure ion mobility spectrometry was used to study both G and V agents.[612] These species were also analyzed in the presence of vesicant derivatives. The lowest limits of detection were found to be <1 ppm. There was a report involving phosphonothioates in which MS was used to determine the products after treatment with Na(s).[597] The formation of the phosphonic acids and phosphonothioic acids could be confirmed. Solid-phase microextraction of VX was used in tandem with GC-MS.[500] The interesting disulfide derivative [bis(diisopropylaminoethyl)disulfide] was determined from a soil sample (detected at 1 μg per 1.0 g of soil).[499] In 2003, secondary ionization (IM-TOF-MS) was used by Steiner et al. in detecting DMMP, pinacolyl methylphosphonate, diethyl phosphoramidate, and 2-(butylamino)ethanethiol.[613] The metabolites of sarin were detected by positive ion chemical ionization as per a report from 2004.[580] A general reference on the technique of desorption mass spectroscopy was presented by Takats and co-workers in 2004.[614] Lastly, some reports involve the mention of pesticides: malathion was studied with GC-FID.[598]

ES-MS was used to support microsynthesis of various *O,O*-dialkyl-*N,N*-dialkylphosphoramidates to generate a library of mass spectra.[615] Additionally the methyl esters of *N,N*-dialkylaminoethane-2-sulfonic acids (DAESAs), R$_2$NCH$_2$CH$_2$S(═O)$_2$OCH$_3$, were analyzed by GC-EI mass spectroscopy.[599] This is similar to a report by D. Pardasani in which the methyl esters of *N,N*-dialkylaminoethane-2-sulfonic acids were detected.[616] Next, aerosol matrices of DMMP, DEEP, DEPA, and DEP were studied using ion mobility time-of-flight mass spectrometry.[617]

Instrument port fluorination was used in a MS experiment with acids (AAPAs and APAs). These analyses gave the respective fluorinated products with detection limits stated as 0.5−800 ng mL^{-1}. A qualitative method was developed for the determination of degraded products of nerve agents through the use of ion-pair liquid chromatography−electrospray ionization tandem mass spectrometry (IP-LC-ESI-MS).[618] Next, alkylphosphonic acids were studied with an ion-pairing agent (*n*-Bu)$_3$N; this was done with a variety of instrumental variations.[618] Generally,

alkylphosphonic acids (APAs) and *O*-alkyl alkylphosphonic acids (AAPAs) give deprotonated molecular ions in the negative mode $[M - H]^-$. With tri-*n*-butyl amine as an ion-pairing agent, a detection limit was quoted as 0.5−10 μg mL^{-1}. Also, amino alcohols (*N*,*N*-diisopropylethanolamine, triethanolamine, *N*-methyldiethanolamine, *N*-ethyldiethanolamine, *N*,*N*-dipropylethanolamine) were studied with *N*,*N*-dialkylaminoethane-2-ols and alkyl *N*,*N*-diethanolamines in the context of extraction and MS.[488] The best limits of detection were reported as 0.01 and 5×10^{-3} μg mL^{-1} (selected ion mode). This method was also used in the analysis of water samples sent by the Organization for Prohibition of Chemical Weapons; human plasma was also analyzed. Next, GC MS was used in conjunction with microextractions that involved hollow fiber (HF-LPME) derivatives. The limits of detection were 0.04−0.36 μg L^{-1}.[503] This involved derivatization and the hydrophobicity of the tube protected the analyte from hydrolysis. DMMP was studied by a femtosecond laser pulse (TOF-MS) in which the ratio of the Me^+ or MeO^+ ionization fragments could be controlled.[576]

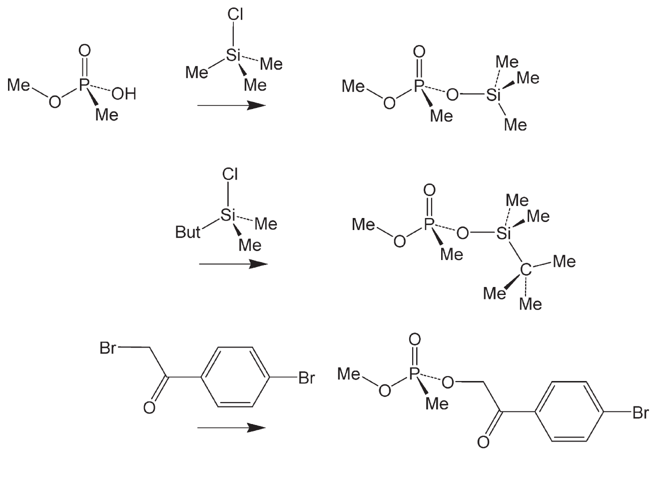
For rapid sensing of all CWA's, Seto and co-workers in 2006 recommended combining the use of a monitoring tape method and counterflow introduction atmospheric pressure chemical ionization mass spectrometry, to be used in conjunction with commercial detection equipment. A new MALDI−TOF method was described to determine the presence of degradation products in isopropyl methylphosphonic acid, pinacolyl methylphosphonic acid, ethyl methylphosphonic acid, isobutyl methylphosphonic acid, and cyclohexyl methylphosphonic acid.[584] Finally, degradation products could be determined using IM-TOF-MS in the negative mode.[619]

The portable ion mobility spectrometer with ^{63}Ni was used for the detection of vapors of sarin, soman, cyclohexylsarin, tabun, and nitrogen mustard 3 with the limit of alarm of 0.005−0.5 mg·m^{-3}.[620] For detection enhancement by HPLC coupled with ICP-MS, Caruso used calcium chloride and ammonium hydroxide for removal of inorganic phosphate as a major interferent.[621] Also, field-portable GC-MS with a transmission quadrupole and cylindrical ion trap is used for the detection of VX-related compounds.[622] Tandem capillary GC-MS and desorption electrospray ionization MS (DESI-MS) are also used.[623,624]

In the Lockridge research group, organophosphorus agent-labeled proteins were treated with trypsin giving the peptides a labeled tyrosine. The MS-MS spectrum followed by separation with HPLC gives the parent ion peaks with diisopropylfluorophosphate (216 amu), sarin (214 amu), and soman (214 amu).[625] For the stable buffer condition, TRIS and TES are treated as buffer compounds with nerve agents for the characterization by LC-EMI-MS.[626] Also, Morokuma suggested the chemical ionization mass spectrometry detection of diethylmethylthiomethylphosphonate (DEMTMP) through theoretical calculations. He considered proton affinity, fluoride affinity, and ionization potential as factors.[627] Recently, a new ^{241}Am ionization aspiration type ion mobility spectrometer was used for the detection of nerve agents in general.[628]

7.10.3. Silylation Agent Studies. The facile reaction of a phosphonic acid and trialkylhalide (e.g., TMSCl, Me_3SiCl) to afford a phosphonic silyl ester allows for a stable and volatile nerve agent derivative for mass spectrometric experiments. There are a variety of reports regarding various silylations as well as other derivatizations. First, a series of [RO(OH)P═O(Me)] derivatives was silylated with $CF_3(C{=}O)N(SiMe_3)_2$ and 1% Me_3SiCl used in derivatization, see Scheme 34.[491] These samples were

Scheme 34. Silylation of MPA with TMSCl or ^{t}BuMe$_2$SiCl



extracted from water, soil, and other media. DMMP was also studied. Next, -SiMe$_2{}^t$Bu derivatives of EMPA, IMPA, PMPA, and MPA were studied in model aqueous soil extraction.[629] Interestingly, this derivatization was impeded by the presence of Ca^{2+} and Mg^{2+} in the presolution. In determining the hydrolysis of VX in equimolar water, the acids were functionalized to their $SiMe_3$ (TMS) counterparts to facilitate analysis.[604] In 2001, derivatization using $SiMe_3$ was also studied by X. Y. Hu and co-workers.[630] Herein, six hydrolysis products of five species were derivatized allowing for detection limits of ∼0.02 mg L^{-1}. Next, a report describes RO(P═O)Me(OH) (R = H, ethyl, isopropyl, and pinacoly groups) species treated to give the corresponding [^{t}BuMe$_2$Si-] derivatives.[631] This derivatization was performed with aqueous samples that included beverages (cola and coffee). Separately, methylphosphonate (MPA) and ethyl, isopropyl, and pinacolyl methylphosphonate were detected via derivatization using [^{t}BuMe$_2$Si-] and studied as soil samples.[588] Next, GC-ICP-MS was used in identifying silylated versions of species that included ethyl methylphosphonic acid, isopropyl methylphosphonic acid, the sodium salt of ethyl hydrogen dimethylamidophosphate, isobutyl hydrogen methylphosphonate, as well as pinacolyl methylphosphonic acid, methylphosphonic acid, and cyclohexyl methylphosphonic acid. In particular, *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide was detected at levels of less than 5 pg.[601] Here *tert*-BuMe$_2$SiCl (TBDMSCl) was used in forming the silylated, and thus more volatile, derivatives from species present in water and soil samples, as confirmed by GC-time-of-flight mass spectrometry (TOF-MS). In another study, phosphonic acids (silylated) were detected in the presence of interferents in the form of pesticide degradation products using GC ICP-MS.[582] The species used were (^{i}PrO)(OH)P═O(Me), (Cyhex(cyclohexyl)O)-(OH)P═O(Me), (pinnacol-O)(OH)P═O(Me), and $(OH)_2$P═O(Me). Three pesticide-based interferents (mixtures of pesticides and silylated degradation products) were prepared in the presence of one silylated species. The TMS derivative of EA-2192 was detected GS-MS analysis.[632]

Other derivatization agents have been used to enable signature readings in mass spectrometry as well. These include bromophenacyl bromide (Scheme 34); this study involved (FAB) LC-MS and LC-MS-MS analysis with EMPA, IPMPA, and PMPA.[587] Limits of detection were reported at 1−20 ng mL^{-1}. Another

example involves derivatization with fluorinated phenyldiazomethane reagents.[633] Detection limits were between 5 and 10 ng mL^{-1}.

7.10.4. Use of Mass Spectroscopy in Phosphorylation of AChE. MS data also finds obvious use in determining AChE conjugation. One study involves tabun and butyl tabun and demonstrates P−N bond cleavage upon AChE binding.[69] Another report explores tabun resistance and an antidote. The report included crystallographic analysis.[596] In this effort, one objective is to determine the amount of NA aging that has taken place with the enzyme. The pathways of phosphorylation and aging were addressed through a paper in 2001 using MALDI-TOF and involving methamidophos and tabun.[70] This involved the use of a hexadeutero form of tabun $(EtO)(CN)P{=}O(N(CD_3)_2)$, which allowed for detection of two adducts with a mass difference of 6.05. After aging, the conjugates possessed the same molecular weight. Furthermore, the aging products of tabun−AChE and paraoxon−AChE had the same molecular weight according to the MS results.

7.10.4.1. Animal Models, Biological Studies and Biomarkers, in Vivo, for Example, the Blood Pool. Various mass spectrometric techniques greatly facilitate *in vitro* and *in vivo* animal studies, especially by detection of known biomarkers stemming from OP intoxication.[28] An early report studied the bioaccumulation of agents in bivalves (clams).[586] Also there were some clinical trials with pigs tested with soman.[593] In these studies, agents themselves (not degradants) could be detected in blood and cerebral spinal fluid (CSF). Interestingly, the levels, and thus the toxicokinetics, of the four isomers of soman could be monitored separately with GC-HRMS: "The relatively non-toxic C(±)P(+) isomers disappeared from the bloodstream and CSF within the first minute, whereas the levels of the highly toxic C(±)P(−) isomers could be followed far longer, depending on the dose." In human and rat serum, fluoridation of the VX degradant provided $(EtO)MeP{=}O(F)$ as a biomarker.[495] Furthermore, the decadeuterated diethyl ethyl phosphonate $((EtO)_2P{=}O(Et))$ was used as an internal standard. Also, with human plasma as a model medium, $(RO)(OH)P{=}O(Me)$ and $(OH)_2P{=}O(Me)$ were reported detected at a limit <22 $\mu g\ L^{-1}$. TMS silylation was effected for six degradation products.[489] Later, in a report by Black and co-workers, albumin tyrosine was phosph(or)ylated.[579] *In vitro* (guinea pigs), this was revealed as a biomarker. It was determined that VX requires higher concentrations to effect phosphorylation. The reasons were not mentioned, but it could be simply due to sterics. Also, soman was detected in plasma using a rat model.[594] The effect of VX skin contact was studied using the guinea pig model.[602] GC-MS-MS was used to monitor VX concentration. Additionally, in an animal experiment, administration of synthesized 2-diisopropylaminoethanethiol (DAET) to rats, resulted in the production of DAEMS. These results documented that GC-MS and GC-MS-MS were applicable to biological samples such as serum. MALDI-TOF was also used.[583,602] Also, guinea pigs, rhesus monkeys, and human plasma were studied.[634] The limit of detection was reported as 0.5 ng mL^{-1}. In 2008, tubulin, a protein commonly studied in the context of mitosis and neurodegenerative diseases, was determined to be affected by tyrosine activation.[578] In a minipig model, plasma was used in studying $(^{i}PrO(P{=}O)Me(OH))$ and cyclohexyl-$O(P{=}O)Me(OH)$. In another study, albumin was studied; peptide fragments of human serum albumin were analyzed in response to chlorpyrifos oxon, dichlorvos, diisopropylfluorophosphate (DFP), and sarin.[578,583,635] The surface tyrosine (residue 411) in albumin was determined to be phosphorylated by analysis of a series of fragments, along with the phosphorylated fragments. Similar research was done in 2010 by H. John for sarin, soman, tabun, cyclosarin, VX, Chinese VX, Russian VX, chlorpyrifos-oxon, DFP, paraoxonethyl, and profenofos.[636] LC-MS/MS was also used as detection technique for VX in blood plasma and microdialysates.[637,638] Chiral quantification of tabun enantiomers in swine blood was carried out by O. Tenberken by GC-PCI-MS.[639] Developed GC-MS can allow for the detection of nerve agents at an exposure level of 1% BuChE inhibition, where ChE activity assay cannot be verified.[640]

7.10.4.2. Urine. The ability to probe for agent and agent metabolites in urine is of great utility and was also investigated in various studies.[641] Tandem MS was used in determing nerve agent metabolites in samples of human urine.[641] Also there was another study detecting the metabolites of sarin, soman, VX, R-VX, and cyclosarin using LC-MS-MS.[494] A general limit of quantitation was given to be ≤0.5 ng mL^{-1}. Furthermore LC-MS-MS was used in another human urine study in which alkyl methylphosphonic acids were studied.[581] A lowest limit of detection was reported as 30 pm mL^{-1}.

7.11. Piezoelectric Crystal Surface Acoustic Wave (SAW) Sorption Detection Devices and Coatings

Surface acoustic wave (SAW) sorption detectors are an important class of detection device currently incorporated into numerous portable devices.[642−645] The contributions of analytical chemists such as J. W. Grate and others are significant.[646] Grate's recent *Chemical Review*, "Acoustic wave microsensor arrays for vapor sensing", along with citations therein, can serve as a reference to the numerous companies employing this kind of technology. An estimated million SAW devices are produced every year and are exemplified by the BAE ChemSentry system or Sandia's hand-held MicroChemLab device. These represent the state of the art. The BAE system was tested against various analytes as reported in the Japanese literature.[91]

There are early relevant papers pertinent to organophosphonates from G. Guilbault and co-workers.[647−653] In this research, the piezoelectric crystal surface is often coated to have a specific interaction with the analyte in question. There have also been reports of efforts to improve such coatings.[536,537,654−656] An acoustic resonator coated with poly(vinylidene fluoride) was used as a nerve agent sensor.[657] The sensitivity of this sensor was as high as 80 kHz/ppm. Thus, the success of a discerning polymer (coating) and one that is selective employs molecular and atomic level interactions; aberrant nonagent interactions may lead to false positives. Understanding metal binding for a wider array of sorption detectors is important to the design of new SAW devices for urgent sensing applications.[440,658,659] The contributions of Guilbault begin in 1972 in which a quartz crystal with various inorganic coatings was tested for responses with DIMP and paraoxon.[648] The next paper in 1974 dealt with oxime coatings and again with DIMP and paraoxon.[649] This progression led to discrete groups of studies that are discussed below. With this method, a large range of dilutions is possible.[660]

7.11.1. Metal Ion Containing Coatings. Some reports have considered metal ions in the coatings, which allow for specific agent binding. A 1981 G. G. Guilbault paper deals with coatings that involve copper complexes for DIMP binding.[650] Before this, Guilbault and co-workers screened a large number of metal chloride salts (MCl_n) with diisopropyl methylphosphonate (DIMP) as a gas analyte (and OP-NA simulant) for sensor

precursors.[661] Guilbault demonstrated that Cu^{2+} binding to DIMP was possible in these arrays. Binding has been investigated as a platform for OP sensing. They used some analytes for (realistic) interferants such as automobile exhaust. Other complexes were evaluated such as those of Ni, Co, and Fe, but Cu^{2+} gave the best response. Also, the ligand had to accommodate enough vacancy.[650,662] Thus, at this early point it was concluded that "copper complexes may adsorb and desorb phosphorus esters in air."[650] Also an uncoated species was determined as well.[651] In 1992, Kepley reported a monolayer that incorporated Cu^{2+} ions.[663] In this SAW array (used because of mass sensitivity), an Au layer was used, combined with a thiolate with a pendant carboxylate group ($-SCH_2(CH_2)_nCOO^-$). A layer exists here with some semblance to a coordinatively unsaturated Cu^{2+} ion surface. Interestingly, for this sensor array, there was a slow response obscured for exposure to water. DIMP was used, and greater monolayer disorder was found with acid-terminated groups than with an alkyl terminated group. The sensitivity was reported as 100 pg/cm^2 of adsorbed substrates. Methylene C−H stretches were assigned in the IR spectrum, as well as C═O stretches (1740, 1717 cm^{-1}). One signal was for a free carbonyl group, while the other corresponded to a CO group engaged in hydrogen bonding. Upon Cu^{2+} complexation bands arise at 1609 and 1450 cm^{-1}. These signals were assigned to the coordinated DIMP: P−O 1016 cm^{-1}, [P−O···H] 1206 cm^{-1}. Another example of utilizing Cu^{2+} ion layers is the report by D. Chen.[664]

Nieuwenhuizen and co-workers explored lanthanide systems for SAW detection platforms.[659,660,665−667] Some common ligand systems appear below that connect with these reports. A report of a SAW device involving La^{3+} describes a molecular ligand based on the common aminocarboxylate framework: *N*,*N*,*O*-tricarboxymethyl tyrosine (TCMT), *N*,*N*-dicarboxymethyl glutamic acid (DCMG), and 2-bis(carboxymethyl)aminohexadecanoic acid (BHA) (Figure 23). This ligand allows for a gas-phase analyte to bind to the surface most likely through its phosphoryl oxygen. This interface interaction gives rise to a change in device mass that is detected by a change in vibrational frequency.[666] Next, Nieuwenhuizen and co-workers published a series of studies of SAW sensors with La^{3+} at the chemical interface in which sarin and DMMP were analyzed.[659] Normalized to the area mass, the BHA ligand, when treated with 5 ppm of DMMP, gives a value of 28.0 Hz/(ppm·μg), whereas, the LaTCMT species gives 4.5 and DCMG gives 5.3 Hz/(ppm·μg). The detection limit of 0.1 ppm was reported with these interfaces. They also reported variable temperature trials involving LaBHA values of 8.2 (30 °C), 3.2 (50 °C), and 1.4 (70 °C) Hz/(ppm·kHz) (sensitivity). At a 5 ppm level of DMMP, when the chemical interface material is $LnCl_3$, there is a sensitivity of 0.2 Hz/(ppm·kHz), with a sensor involving LaBHA a sensitivity of 1.1, and with only BHA a sensitivity of 0 Hz/(ppm·kHz). Reliability and accuracy is less when just BHA is used. Some damage is incurred by GB to the chemical interface. In these studies EtOH, *n*-hexane, methyl ethylketone, ethyl acetate, toluene, water, ammonia, and nitrogen dioxide were studied for their possible intereference capacity. Interestingly, NO_2 reacts strongly with a sensitivity of 3.6 Hz/(ppm μg). A paper by C. Dejous deals with variable-temperature reversible sensing at concentrations of 10−100 ppm.[668] A R. M. Crooks paper dealt with surface exposure to DiMP.[669,670] The surface coverage was estimated to possess a thickness of 16 monolayers, with a proposed binding that involved Cu^{2+} ions.[669] Next, a miniature sensor was prepared to determine the concentration of

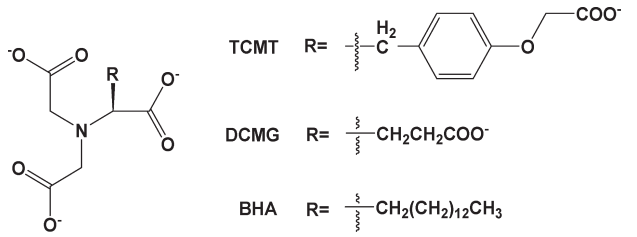


Figure 23. Ligands used by Nieuwenhuizen and co-workers.[666]

DMMP as it passes through a filter bed (porous carbon).[671] Here, the throughput level and humidity range were tested. Metal oxides, such as TiO_2 and MnO, are also applied on quartz crystal microbalance sensors.[672,673] DMMP species were tested with these sensors. Next, there was a report dealing with preconcentrator sampling,[674] capillaries for preconcentrating,[675] multisensor systems,[676] and a study of a variety of coatings.[677] There was also a GC-SAW method explored for sarin and soman.[678]

7.11.2. Hydrogen Bonding: Organic Coatings. Four reports by C. Hartmann-Thompson and co-workers describe coatings that utilize hydrogen bonding. The first one involved hyperbranched polymer coatings for SAW applications for DMMP; a phenol derivative was found to be more effective than the hexafluoro-2-propanol group.[536] This was followed by a 2006 "letter" that underscored the advantages of modifiable H-bonded arrays.[679] A report describing derivatives involving oligosilsesquioxane (Figure 24) nanofiller compounds also appeared.[537] The fourth article involved two types of possible hydrogen bonds for DMMP.[656] There are related reports by other groups as well. In one report, there was a SAW sensor in which the delay line was coated.[668] DIMP was analyzed in a SAM−SAW device. Also, in a somewhat related report, the photoacoustics of diethyl methylphosphonate, DMMP, diisopropyl methylphosphonate, and diethyl phthalate (DEP) were studied.[680] Siloxane polymer functionalized with hexafluoroisopropanol groups was synthesized for use with a quartz crystal microbalance sensor to detect DMMP. The detection limits of this sensor were as low as 0.13 ppm.[681]

7.11.3. Cantilever Devices. Cantilever beams, in the context of metal-oxide semiconducting research, have been reported.[682,683] Another cantilever device involved the use of PZT to detect DMMP.[339] Also, a microcantilever-based "electronic nose" was developed for the determination of concentration of DMMP in binary and ternary mixture.[684] Lastly, a microcantilever piezoresistive sensor consisting of SiO_2 functionalized self-assembled bilayers was reported.[685]

8. CONCLUSIONS AND CRITICAL ASSESSMENT

While this review describes many mainstream efforts by various chemical and biochemical laboratories, there are also many smaller sets of studies and single papers that investigate new systems undertaken in the hope that informative or useful results can be obtained. The value of these many "one hits" is unclear. What we need, really, is a quantum leap in this research; this will come through introduction of new or hybrid techniques, as well as by better connection of the dots between existing sets of studies. Further, we should look at new developments areas such as new families of materials, nanoscience, and enzymology as they continue to evolve. In Scheme 35, we tried to graphically summarize many of the

topics that were discussed herein with the larger picture in mind. Clearly, there is a lifetime for agents as well as for human individuals. Contamination of agents during their lifetime (synthesis, storage, unwanted deployment, and finally destruction or decontamination) impacts human health and the environment. Recourses such as monitoring, detection, and sensing are important and should be further developed; this review has intended to provide a basis for this. Below, we outline areas for future efforts and foci in protection, decomposition, decontamination, and sensing.

8.1. Decomposition

Systems based on microorganisms are essential to be included in a discussion of decontamination. It is here where we inevitably lose focus on molecular level events. While there is indirect evidence of selective bond cleavage, it would be very helpful to be able to verify mechanisms at the molecular and atomic level. Such information could confirm the action of a specific enzyme and allow for clearer understanding of the mild and intrinsically "less disruptive" degradation pathways of microorganisms/enzymes, especially for cleavage of the hydrolytically stable P−C bond. This bond is acid and base stable and more thermally resistant to decomposition. One general drawback is selectivity for the analyte in question: these studies do not always demonstrate that microorganisms will *preferably* use organophosphonates in any given situation. Thus, if there is only a certain, specific, pesticide, then the enzyme has no choice but to use it as a nutrient. Another negative point is that such exemplary systems *do* require a great amount of protein engineering, and perhaps, large amounts of biomaterials, which would require stringent handling. Compared with the robustness of small molecule catalysts, the microbial systems are quite sensitive. The microbial and enzymatic studies involve an exploration of mechanism, but sometimes do not account for which amino acids are key in the active site. Such reports also do not always comment on the reusability of microbes or adaptation for use under various conditions.

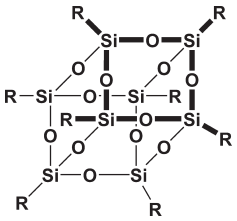


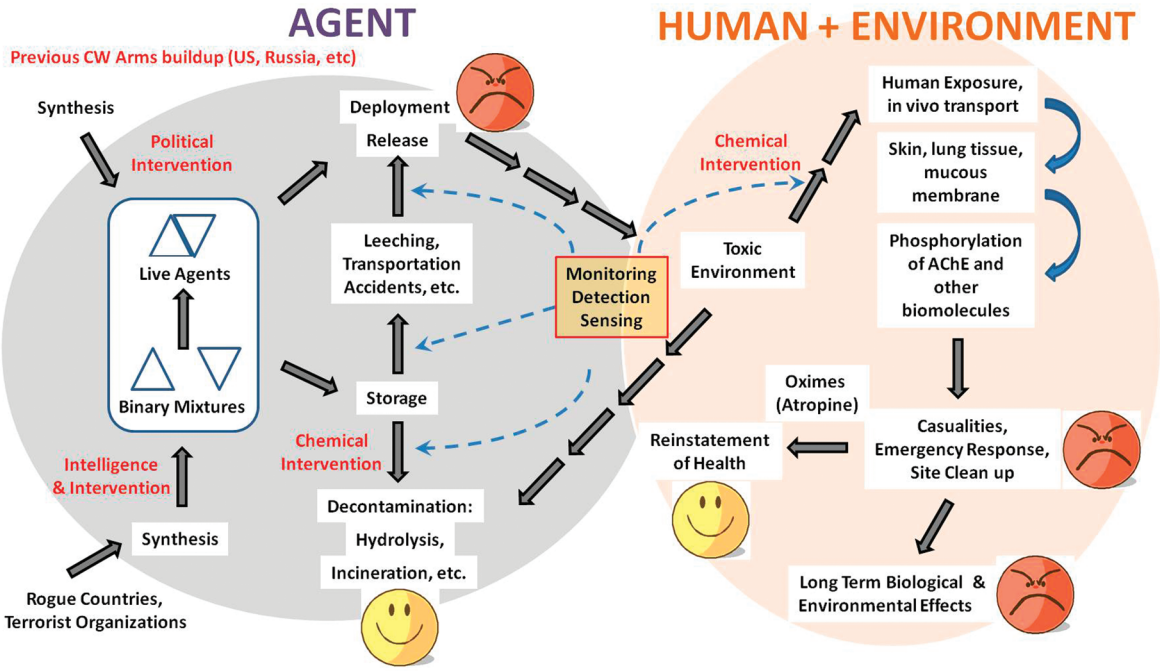
Figure 24. The idealized structure of the oligosilsesquioxane.

It might seem that bacterial engineering has run its course: it is expensive, is temperature sensitive, and requires meticulousness in understanding cell biology. However, the amount of insight and control one has with this technology is underscored by the *Pseudomonas putida* report by de la Peña Mattozzi among others, which signifies the potential elegance and importance of future related work. As with other studies of this kind, mild conditions can be employed and *complete degradation* is approached through interfering microorganisms. Importantly, the presence of bacteria in chemical studies might obfuscate the results. So we underscore the importance of careful analysis (perhaps more cleanliness in chemistry). *We need more detailed studies that follow real NAs from full agent down to completely degraded materials.* Cellular biology will play an important role in designing further hybrid systems.

8.2. Decontamination

Large scale treatments have included self-cleaning coatings. Also "clothing" and new materials remain a challenge, especially

Scheme 35. Sketch Connecting Aspects of Agent Development, Storage and Environmental Impact to Insights into What Is Known about *in Vivo* Transport



CHEMICAL INTERVENTION AT THE INTERFACE OF SYNTHETIC NERVE AGENT (ORGANOPHOSPHONATE) AND HUMAN LIFECYCLES

dx.doi.org/10.1021/cr100193y |*Chem. Rev.* 2011, 111, 5345–5403

in terms of characterization. New materials such as those at surfaces are probably more promising for a greater range of applications than particles. A very important topic for the study of the decomposition of nerve agents and closely related compounds is still solid phase surfaces. This area of research continues to represent a frontier and is a likely area of future growth. In light of the enormous amount of research being conducted on the morphologies of new nanometer-sized materials, chemical possibilities abound at surfaces, phase boundaries, edges and apexes, clusters, microparticles, and nanoparticles, as well as tailored surfaces. Foremost, the particle approach in catalysis gives the exceptional and well-documented advantages of enhanced surface area and increased "concentration" of edges/corners. The presence and variation of defects, absences, and material pores may also supply critical microstructure for catalytic enhancement. Imaging of these particles is also better and more detailed than ever before, due to improvements in and more widespread use of TEM and SEM.

8.3. Sensing

Fluorescence and colorimetric techniques have limitations in terms of the photostability of the sensor and the accessible wavelengths. New techniques in spectroscopy will enable a revisitation of the catalysis of NAs on surfaces as well as probing them directly in solution or in the gas phase. We are still waiting for the next spectroscopic technique and equipment that facilitate the study of *real* agents under *real* time scales, in the context of *real* matrices.

8.4. Protection

The most important consideration in protection is separating the agent from personnel. Optimal personal protection has yet to be realized. But importantly, we can use new markers; personnel need to know they are out of harm's way. Wearable convenient clothing that can sense in real-time and degrade contaminants is an important frontier that has not yet been crossed because of limitations in characterization and experimental conditions. Efforts in this and other areas continue.

8.5. Critical Needs

Meetings and committees are important to bring the best options before a group of experts in the field. Eventually, the chosen techniques can be ready to implement. Continued vigilance in the pursuit of a greater understanding of organophosphonate sensing and decontamination can be found in recent society events. Each year, there is a Chemical and Biological Defense Science and Technology Conference meeting (DTRA) (http://cbdstconf.sainc.com). Also, at the ACS meeting in Washington in 2009, the Inorganic division presented a symposium entitled "Sensing and Destroying Chemical Nerve Agents and Pesticides".[686] Continued interdisplinary and collaborative meetings will allow for better progress, as underscored by the recent papers in high impact journals and in the patent literature reviewed here. Interdisciplinary work and discussions focused on real agents is at the heart of basic and applied research advances. A common forum for sensors and decontamination agents is also vital for effective communication between various scientists in the field.

AUTHOR INFORMATION

Corresponding Author

*E-mail: dchurchill@kaist.ac.kr. Phone: +82-42-350-2845. Fax: +82-42-350-2810.

BIOGRAPHIES

Kibong Kim was born in Seoul, South Korea, in 1984 and moved to Daejeon to pursue his undergraduate studies at KAIST in 2002. He obtained his B.S. degree in Chemistry in 2006 and is currently a Department of Chemistry Ph.D. candidate at KAIST under the guidance of Prof. David G. Churchill. His research focuses on molecular recognition involving fluorescent platforms explored through synthesis, photophysical studies, NMR spectroscopy, and DFT calculations.

Olga Tsay was born in Tashkent, the capital of Uzbekistan, then part of the former Soviet Union. She received her B.S. degree (1999) and M.S. degree (2001) in chemical technology and biotechnology in the laboratory of Professor Michael A. Grin at the Moscow State Academy of Fine Chemical Technology named for M. V. Lomonosov in Moscow, Russia. After graduation, from 2001 to 2005, she worked as an organic chemist at ASINEX, Ltd., in Moscow. Currently she is pursuing her Ph.D. degree under the supervision of Professor David G. Churchill at KAIST. Her synthetic chemistry research focuses generally on molecular aspects of neurodegenerative diseases; so far she has done research on chiral corrole complexes and their use in molecular recognition.

ACS Meeting, Salt Lake City: Photo by Gregory H. Robinson.

David Allan Atwood (right) was born in 1965 in Urbana, IL, while his father Jerry Atwood was in graduate school at the University of Illinois. At an early age David moved to Tuscaloosa, AL, where he grew up and ultimately attended college. After graduation from the University of Alabama, David moved to Austin, TX, to attend graduate school at the University of Texas. In the spring of 1992, he graduated with his Ph.D. degree in Inorganic Chemistry under the skillful guidance of Richard A. Jones. From UT, he moved as an Assistant Professor to North Dakota State University as part of their new Center for Main Group Chemistry. In 1998 David Atwood joined the Chemistry Department at the University of Kentucky faculty as an Associate Professor. His research addresses fundamental and applied aspects of the main-group elements. This includes work on chelated group 13 compounds, molecular routes to metal oxide materials, and the design and use of ligands to remediate and mitigate contaminant elements in water.

David George Churchill (left) was born in the Chicago, IL, area in the fall of 1972 but moved to the Buffalo, NY, area before age 3. He obtained a B.S. degree in Chemistry at the University at Buffalo (NY) while performing X-ray crystallographic studies in the laboratory of his father, M. R. Churchill. He then made his way downstate to New York City to spend five years in the chemical laboratories of Professor Gerard (Ged) Parkin at Columbia University (NY). As a graduate student, he earned Departmental distinctions for both teaching (Miller award) and research (Pegram award). After his Ph.D., but before his debut in Asia, D.G.C. served as a postdoctoral fellow for Professor Kenneth N. Raymond in the Department of Chemistry at U. C., Berkeley (CA). Churchill moved to East Asia in 2004 to become the first American to build a tenure track academic career in the Republic of (South) Korea. He was promoted to associate professor in September 2009. His current research deals with aspects of molecular neurodegeneration.

ACKNOWLEDGMENT

D.G.C. acknowledges support from NRF (National Research Foundation) of Korea (Grant Nos. 2009-0070330 and 2010-0013660) and from the Korea Science and Engineering Foundation (KOSEF) (Grant No. R01-2008-000-12388-0). Professor Elizabeth T. Papish (Department of Chemistry, Drexel University) is acknowledged for valuable discussions during the early stage of manuscript preparation. We gratefully acknowledge the pains taken by the referees in reviewing our work and in preparing their comments. We especially thank reviewer 3.

LIST OF ABBREVIATIONS

AChE	acetylcholinesterase (also found as acetylcholine esterase, acetylcholineesterase, etc.)
ASH	activated solution of hypochlorite
ATR-FTIR	attenuated total reflection−infrared Fourier transform spectroscopy
BSA	bovine serum albumin
CB	cannabinoid
CWA	chemical warfare agent
DMMP	dimethyl methylphosphonate
DIMP	diisopropyl methylphosphonate
DS2	decontamination solution 2
ELISA	enzyme-linked immunosorbent assay
GB	sarin; *O*-isopropyl methylphosphonofluoridate
GD	soman; 3,3-dimethyl-2-butyl methyl phosphonofluoridate
GF	cyclosarin; *O*-cyclohexyl methylphosphonofluoridate
CTABr	cetyl trimethylammonium bromide
HI-6	pyridinium, 1-(((4-(aminocarbonyl)pyridinio)-methoxy)methyl)-2-((hydroxyimino)methyl))-, dichloride
HSA	human serum albumin
HTH	high test hypochlorite
IMS	ion mobility spectrometry
IR	infrared
KLH	keyhole limpet hemocyanin
Ln	lanthanide
MALDI-TOF-MS	matrix-assisted laser desorption ionization−time-of flight mass spectrometry
NMR	nuclear magnetic resonance
OP	organophosphonate
OPH	organophosphorus hydrolase
2-PAM	pralidoxime
PET	photoinduced electron transfer
PZT	lead zirconate titanate
RSDL	reactive skin decontaminant lotion
R-VX	*O*-isobutyl-*S*-2-diethylaminoethyl methylphosphonothioate
SAW	surface acoustic wave
SLASH	self-limiting activated solution of hypochlorite
VX	ethyl-*S*-diisopropylaminoethyl methyl phosphothioate
WMD	weapons of mass destruction
WWI	world war I
WWII	world war II

REFERENCES

(1) Smith, B. M. *Chem. Soc. Rev.* **2008**, *37*, 470.
(2) Yang, Y. C.; Baker, J. A.; Ward, J. R. *Chem. Rev.* **1992**, *92*, 1729.
(3) John, H.; Worek, F.; Thiermann, H. *Anal. Bioanal. Chem.* **2008**, *391*, 97.
(4) Kuca, K.; Jun, D.; Bajgar, J. *Curr. Pharm. Des.* **2007**, *13*, 3445.
(5) Bajgar, J.; Fusek, J.; Kuca, K.; Bartosova, L.; Jun, D. *Mini-Rev. Med. Chem.* **2007**, *7*, 461.
(6) Kuca, K.; Jun, D.; Musilek, K. *Mini-Rev. Med. Chem.* **2006**, *6*, 269.
(7) Kuca, K.; Cabal, J.; Sevelova, L.; Jun, D.; Krejcova, G. *Drug Metab. Rev.* **2004**, *36*, 329.
(8) Zhu, H. W.; O'Brien, J. J.; O'Callaghan, J. P.; Miller, D. B.; Zhang, Q. A.; Rana, M.; Tsui, T.; Peng, Y. Y.; Tomesch, J.; Hendrick, J. P.; Wennogle, L. P.; Snyder, G. L. *Brain Res.* **2010**, *1342*, 11.

(9) Eubanks, L. M.; Dickerson, T. J.; Janda, K. D. *Chem. Soc. Rev.* **2007**, *36*, 458.
(10) Smith, S. J. *Talanta* **1983**, *30*, 725.
(11) Talmage, S. S.; Watson, A. P.; Hauschild, V.; Munro, N. B.; King, J. *Curr. Org. Chem.* **2007**, *11*, 285.
(12) Mitra, A.; Atwood, D. A. *Mod. Aspects Main Group Chem.* **2006**, *917*, 390.
(13) Grimsley, J. K.; Disioudi, B. D.; Holton, T. R.; Sacchettini, J. C.; Wild, J. R. *NATO Sci. Ser., 1* **2000**, *33*, 223.
(14) Yang, Y. C. *Acc. Chem. Res.* **1999**, *32*, 109.
(15) Holm, F. W. *NATO Sci. Ser., 1* **1998**, *22*, 159.
(16) Seto, Y. *Yakugaku Zasshi* **2009**, *129*, 53.
(17) Munro, N. B.; Talmage, S. S.; Griffin, G. D.; Waters, L. C.; Watson, A. P.; King, J. F.; Hauschild, V. *Environ. Health Perspect.* **1999**, *107*, 933.
(18) Singh, B. K.; Kuhad, R. C.; Singh, A.; Lal, R.; Tripathi, K. K. *Crit. Rev. Biotechnol.* **1999**, *19*, 197.
(19) Yang, Y.-C. *Chem. Ind.* **1995**, 334.
(20) Olson, B. A.; Conrick, J. E.; Packer, E. B.; Maggio, C. *Proceedings, 89th Annual Meeting, Air & Waste Management Association*; Air & Waste Management Association: Pittsburgh, PA, 1996; wp9402/1.
(21) Bartelt-Hunt, S. L.; Knappe, D. R. U.; Barlaz, M. A. *Crit. Rev. Environ. Sci. Technol.* **2008**, *38*, 112.
(22) Gianfreda, L.; Rao, M. A. *Enzyme Microb. Technol.* **2004**, *35*, 339.
(23) Russell, A. J.; Kaar, J. L.; Berberich, J. A. *The Bridge* **2003**, *33*, 19.
(24) Black, R. M. *J. Chromatogr. B* **2010**, *878*, 1207.
(25) Anzai, J. I. *Yakugaku Zasshi* **2006**, *126*, 1301.
(26) Simonian, A. L.; Flounders, A. W.; Wild, J. R. *Electroanalysis* **2004**, *16*, 1896.
(27) Russell, A. J.; Berberich, J. A.; Drevon, G. E.; Koepsel, R. R. *Annu. Rev. Biomed. Eng.* **2003**, *5*, 1.
(28) Noort, D.; Benschop, H. P.; Black, R. M. *Toxicol. Appl. Pharmacol.* **2002**, *184*, 116.
(29) Young, R. A.; Opresko, D. M.; Watson, A. P.; Ross, R. H.; King, J.; Choudhury, H. *Hum. Ecol. Risk Assess.* **1999**, *5*, 589.
(30) Munro, N. B.; Ambrose, K. R.; Watson, A. P. *Environ. Health Perspect.* **1994**, *102*, 18.
(31) Benschop, H. P.; De Jong, L. P. A. *Acc. Chem. Res.* **1988**, *21*, 368.
(32) Brickhouse, M. D.; Matteson, R.; Durst, H. D.; O'Connor, R. J. *Proceedings of the ERDEC Scientific Conference on Chemical and Biological Defense Research, Aberdeen Proving Ground, MD, United States, Nov. 17−20, 1998*; 1999; p 591. Ed. By D. A. Berg, National Technical Information Service, Springfield, VA. USA.
(33) Ekerdt, J. G.; Klabunde, K. J.; Shapley, J. R.; White, J. M.; Yates, J. T., Jr. *J. Phys. Chem.* **1988**, *92*, 6182.
(34) Edmundson, R. S. *Organophosphorus Chem.* **1983**, *14*, 123.
(35) Morales-Rojas, H.; Moss, R. A. *Chem. Rev.* **2002**, *102*, 2497.
(36) Wagner, G. W.; Procell, L. R.; Yang, Y. C.; Bunton, C. A. *Langmuir* **2001**, *17*, 4809.
(37) Hierlemann, A.; Gutierrez-Osuna, R. *Chem. Rev.* **2008**, *108*, 563.
(38) Gopel, W.; Hesse, J.; Zemel, J. N. In *Sensors. A Comprehensive Survey*; Wiley-VCH: New York, 1989; Vol. 2, p661.
(39) *Chemical and Biological Warfare*; Rose, S., Pavett, D., Eds.; Beacon Press: Boston, 1969.
(40) Newmark, J. *Neurology* **2004**, *62*, 1590.
(41) Romano, J. A.; Lukey, B. J.; Salem, H. *Chemical Warfare Agents: Chemistry, Pharmacology, Toxicology, and Therapeutics*, 2nd ed.; CRC Press: Boca Raton, FL, 2008.
(42) Refer to Lois R. Ember's epic series of articles in *Chemical & Enginering News* for governmental policy, etc.
(43) Degenhardt, C. E. A. M.; Van Den Berg, G. R.; De Jong, L. P. A.; Benschop, H. P.; Van Genderen, J.; Van de Meent, D. *J. Am. Chem. Soc.* **1986**, *108*, 8290.
(44) Krejcova, G.; Kuca, K.; Sevelova, L. *Def. Sci. J.* **2005**, *55*, 105.
(45) Balmer, B. *Soc. Stud. Sci.* **2006**, *36*, 691.
(46) Aurbek, N.; Thiermann, H.; Szinicz, L.; Eyer, P.; Worek, F. *Toxicology* **2006**, *224*, 91.
(47) Kenttamaa, H. I.; Cooks, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 1881.
(48) Griffiths, J. E.; Burg, A. B. *J. Am. Chem. Soc.* **1960**, *82*, 1507.
(49) Cummings, D. A.; McMaster, J.; Rieger, A. L.; Rieger, P. H. *Organometallics* **1997**, *16*, 4362.
(50) Sokolov, M. N.; Virovets, A. V.; Dybtsev, D. N.; Chubarova, E. V.; Fedin, V. P.; Fenske, D. *Inorg. Chem.* **2001**, *40*, 4816.
(51) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon Press: Oxford, U.K., 1984.
(52) Griffiths, T. R.; Volkovich, V. A.; Carper, W. R. *Struct. Chem.* **2010**, *21*, 291.
(53) Lin, S. T.; Klabunde, K. J. *Langmuir* **1985**, *1*, 600.
(54) Eto, M. *Organophosphorus Pesticides: Organic and Biological Chemistry*; CRC Press, Inc: Cleveland, OH, 1974.
(55) Mccoy, M. *Chem. Eng. News* **2009**, *87* (July 20), 36.
(56) Mandal, D.; Mondal, B.; Das, A. K. *J. Phys. Chem. A* **2010**, *114*, 10717.
(57) Friboulet, A.; Rieger, F.; Goudou, D.; Amitai, G.; Taylor, P. *Biochemistry* **1990**, *29*, 914.
(58) Albaret, C.; Lacoutiere, S.; Ashman, W. P.; Froment, D.; Fortier, P. L. *Proteins: Struct., Funct., Genet.* **1997**, *28*, 543.
(59) Shih, T. M.; Kan, R. K.; McDonough, J. H. *Chem.-Biol. Interact.* **2005**, *157*, 293.
(60) Delfino, R. T.; Ribeiro, T. S.; Figueroa-Villar, J. D. *J. Braz. Chem. Soc.* **2009**, *20*, 407.
(61) Quinn, D. M. *Chem. Rev.* **1987**, *87*, 955.
(62) Ordentlich, A.; Barak, D.; Kronman, C.; Ariel, N.; Segall, Y.; Velan, B.; Shafferman, A. *J. Biol. Chem.* **1996**, *271*, 11953.
(63) *Chemical Warfare Agents: Toxicology and Treatment*, 2nd ed.; Marss, T. C., Maynard, R. L., Sidell, F. R., Eds.; John Wiley & Sons Ltd: West Sussex, U.K., 2007.
(64) Wang, J.; Gu, J.; Leszczynski, J. *J. Phys. Chem. B* **2006**, *110*, 7567.
(65) Majumdar, D.; Roszak, S.; Leszczynski, J. *J. Phys. Chem. B* **2006**, *110*, 13597.
(66) Wang, J.; Gu, J.; Leszczynski, J. *J. Phys. Chem. B* **2008**, *112*, 3485.
(67) Epstein, T. M.; Samanta, U.; Kirby, S. D.; Cerasoli, D. M.; Bahnson, B. J. *Biochemistry* **2009**, *48*, 3425.
(68) Masson, P.; Nachon, F.; Lockridge, O. *Chem-Biol. Interact.* **2010**, *187*, 157.
(69) Barak, D.; Ordentlich, A.; Kaplan, D.; Barak, R.; Mizrahi, D.; Kronman, C.; Segall, Y.; Velan, B.; Shafferman, A. *Biochemistry* **2000**, *39*, 1156.
(70) Elhanany, E.; Ordentlich, A.; Dgany, O.; Kaplan, D.; Segall, Y.; Barak, R.; Velan, B.; Shafferman, A. *Chem. Res. Toxicol.* **2001**, *14*, 912.
(71) Carletti, E.; Li, H.; Li, B.; Ekstrom, F.; Nicolet, Y.; Loiodice, M.; Gillon, E.; Froment, M. T.; Lockridge, O.; Schopfer, L. M.; Masson, P.; Nachon, F. *J. Am. Chem. Soc.* **2008**, *130*, 16011.
(72) Ordentlich, A.; Barak, D.; Kronman, C.; Benschop, H. P.; De Jong, L. P. A.; Ariel, N.; Barak, R.; Segall, Y.; Velan, B.; Shafferman, A. *Biochemistry* **1999**, *38*, 3055.
(73) Casida, J. E.; Quistad, G. B. *Chem. Res. Toxicol.* **2004**, *17*, 983.
(74) Segall, Y.; Quistad, G. B.; Sparks, S. E.; Nomura, D. K.; Casida, J. E. *Toxicol. Sci.* **2003**, *76*, 131.
(75) Gessa, G. L.; Mascia, M. S.; Casu, M. A.; Carta, G. *Eur. J. Pharmacol.* **1997**, *327*, R1.
(76) Quistad, G. B.; Klintenberg, R.; Caboni, P.; Liang, S. N.; Casida, J. E. *Toxicol. Appl. Pharmacol.* **2006**, *211*, 78.
(77) Quistad, G. B.; Nomura, D. K.; Sparks, S. E.; Segall, Y.; Casida, J. E. *Toxicol. Lett.* **2002**, *135*, 89.
(78) Quistad, G. B.; Sparks, S. E.; Casida, J. E. *Toxicol. Appl. Pharmacol.* **2001**, *173*, 48.
(79) Nomura, D. K.; Blankman, J. L.; Simon, G. M.; Fujioka, K.; Issa, R. S.; Ward, A. M.; Cravatt, B. F.; Casida, J. E. *Nat. Chem. Biol.* **2008**, *4*, 373.
(80) Nallapaneni, A.; Liu, J.; Karanth, S.; Pope, C. *Toxicology* **2006**, *227*, 173.
(81) Jiang, W.; Duysen, E. G.; Hansen, H.; Shlyakhtenko, L.; Schopfer, L. M.; Lockridge, O. *Toxicol. Sci.* **2010**, *115*, 183.

(82) Myhrer, T. *Neurotoxicology* **2010**, *31*, 629.
(83) Black, R. M.; Clarke, R. J.; Read, R. W.; Reid, M. T. J. *J. Chromatogr. A* **1994**, *662*, 301.
(84) Okumura, T.; Ariyoshi, K.; Hitomi, T.; Hirahara, K.; Itoh, T.; Iwamura, T.; Nakashima, A.; Motomura, Y.; Taki, K.; Suzuki, K. *Toxin Rev.* **2009**, *28*, 255.
(85) Zurer, P. *Chem. Eng. News* **1998**, *76* (Aug 31), 7.
(86) Tsuchihashi, H.; Katagi, M.; Nishikawa, M.; Tatsuno, M. *J. Anal. Toxicol.* **1998**, *22*, 383.
(87) Ember, L. *Chem. Eng. News* **1995**, *73* (Mar 27), 6.
(88) Chao, L. L.; Rothlind, J. C.; Cardenas, V. A.; Meyerhoff, D. J.; Weiner, M. W. *Neurotoxicology* **2010**, *31*, 493.
(89) Ember, L. *Chem. Eng. News* **2004**, *82* (May 24), 9.
(90) Ember, L. *Chem. Eng. News* **2004**, *82* (June 14), 15.
(91) Matsushita, K.; Sekiguchi, H.; Seto, Y. *Bunseki Kagaku* **2005**, *54*, 83.
(92) Ember, L. *Chem. Eng. News* **1998**, *76* (Aug 31), 6.
(93) NRC *Occupational Health and Workplace Monitoring at Chemical Agent Disposal Facilities*; National Academies Press: Washington, DC, 2001.
(94) Trapp, R. *Ann. N.Y. Acad. Sci.* **2006**, *1076*, 527.
(95) Ember, L. *Chem. Eng. News* **2008**, *86* (Mar 24), 29.
(96) Ember, L. *Chem. Eng. News* **2003**, *81* (Dec 1), 28.
(97) Hadlington, S. In *Chemistry World*; Royal Society of Chemistry: Cambridge, U.K., 2006; Vol. 3.
(98) Matousek, J. *Ann. N.Y. Acad. Sci.* **2006**, *1076*, 549.
(99) NRC *Alternative Technologies for the Destruction of Chemical Agents and Munitions*; National Academy Press: Washington, DC, 1993.
(100) NRC *Review and Evaluation of Alternative Chemical Disposal Technologies*; Naional Academy Press: Washington, DC, 1996.
(101) Pearson, G. S.; Magee, R. S. *Pure Appl. Chem.* **2002**, *74*, 187.
(102) NRC *Recommendations for the Disposal of Chemical Agents and Munitions*: National Academy Press: Washington, DC, 1994.
(103) U.S. Army's Chemical Material Agency Agent Destruction Status (http://www.cma.army.mil).
(104) NRC *Review of Systemization of the Tooele Chemical Agent Disposal Facility*; National Academy Press: Washington, DC, 1996.
(105) Flamm, K. J.; Kwan, Q.; McNulty, W. B. "Chemical Stockpile Disposal Program. Chemical agent and munition disposal. Summary of the U.S. Army's experience," Chem. Demilitarization, Off. Program Manager, Aberdeen Proving Ground, MD, USA, 1987.
(106) Groenewold, G. S. *Main Group Chem.* **2010**, *9*, 221.
(107) U.S. Army's Chemical Materials Agency, Richmond, KY (http://www.cma.army.mil/bluegrass.aspx).
(108) Irvine, R. L.; Haraburda, S. S.; Galbis-Reig, C. *Water Sci. Technol.* **2004**, *50*, 11.
(109) Marrone, P. A.; Cantwell, S. D.; Dalton, D. W. *Ind. Eng. Chem. Res.* **2005**, *44*, 9030.
(110) Veriansyah, B.; Kim, J. D.; Lee, J. C. *J. Hazard. Mater.* **2007**, *147*, 8.
(111) Farquharson, S.; Inscore, F. E.; Christesen, S. *Top. Appl. Phys.* **2006**, *103*, 447.
(112) Gustafson, R. L.; Martell, A. E. *J. Am. Chem. Soc.* **1962**, *84*, 2309.
(113) Ward, J. R.; Yang, Y. C.; Wilson, R. B., Jr.; Burrows, W. D.; Ackerman, L. L. *Bioorg. Chem.* **1988**, *16*, 12.
(114) Daniel, K. A.; Kopff, L. A.; Patterson, E. V. *J. Phys. Org. Chem.* **2008**, *21*, 321.
(115) Seckute, J.; Menke, J. L.; Emnett, R. J.; Patterson, E. V.; Cramer, C. J. *J. Org. Chem.* **2005**, *70*, 8649.
(116) Crenshaw, M. D.; Hayes, T. L.; Miller, T. L.; Shannon, C. M. *J. Appl. Toxicol.* **2001**, *21*, S3.
(117) Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Rohrbaugh, D. K.; Procell, L. R.; Samuel, J. B. *J. Org. Chem.* **1996**, *61*, 8407.
(118) Wagner, G. W. *Main Group Chem.* **2010**, *9*, 257.
(119) Epstein, J.; Demek, M. M.; Rosenblatt, D. H. *J. Org. Chem.* **1956**, *21*, 796.
(120) Larsson, L. *Acta Chem. Scand.* **1958**, *12*, 723.
(121) Wagner, G. W.; Yang, Y. C. *Ind. Eng. Chem. Res.* **2002**, *41*, 1925.
(122) Khan, M. A. S.; Kesharwani, M. K.; Bandyopadhyay, T.; Ganguly, B. *THEOCHEM* **2010**, *944*, 132.
(123) Kesharwani, M. K.; Khan, M. A. S.; Bandyopadhyay, T.; Ganguly, B. *Theor. Chem. Acc.* **2010**, *127*, 39.
(124) Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Bunton, C. A. *J. Org. Chem.* **1993**, *58*, 6964.
(125) David, M. D.; Seiber, J. N. *Environ. Pollut.* **1999**, *105*, 121.
(126) Kenley, R. A.; Lee, G. C.; Winterle, J. S. *J. Org. Chem.* **1985**, *50*, 40.
(127) Qian, C.; Sanders, P. F.; Seiber, J. N. *Bull. Environ. Contam. Toxicol.* **1985**, *35*, 682.
(128) Wagner, G. W. Transportation, Storage, and Use of Hydrogen Peroxide for CB Decontamination. ECBC-TR-601. Aberdeen Proving Ground, MD, Jan 2008; unclassified report.
(129) See H_2O_2 MSDS sheet and related reports; (JT Baker) http://www.jtbaker.com/msds/englishhtml/h4065.htm, accessed March 2011.
(130) See sodium perborate MSDS sheet and related reports; (JT Baker) http://www.jtbaker.com/msds/englishhtml/s4634.htm, accessed March 2011.
(131) Churchill, D. G. *J. Chem. Educ.* **2006**, *83*, 1798.
(132) Bjarnason, S.; Mikler, J.; Hill, I.; Tenn, C.; Garrett, M.; Caddy, N.; Sawyer, T. W. *Hum. Exp. Toxicol.* **2008**, *27*, 253.
(133) Epstein, J.; Bauer, V. E.; Saxe, M.; Demek, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 4068.
(134) Dubey, D. K.; Gupta, A. K.; Sharma, M.; Prabha, S.; Vaidyanathaswamy, R. *Langmuir* **2002**, *18*, 10489.
(135) Raber, E.; McGuire, R. *J. Hazard. Mater.* **2002**, *93*, 339.
(136) Cassagne, T.; Cristau, H. J.; Delmas, G.; Desgranges, M.; Lion, C.; Magnaud, G.; Torreilles, E.; Virieux, D. *Heteroat. Chem.* **2001**, *12*, 485.
(137) DeBruin, K. E.; Tang, C. I. W.; Johnson, D. M.; Wilde, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 5871.
(138) Yang, Y. C.; Berg, F. J.; Szafraniec, L. L.; Beaudry, W. T.; Bunton, C. A.; Kumar, A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 607.
(139) Wagner-Jauregg, T.; Hackley, B. E., Jr.; Lies, T. A.; Owens, O. O.; Proper, R. *J. Am. Chem. Soc.* **1955**, *77*, 922.
(140) Augustinsson, K. B.; Heimburger, G. *Acta Chem. Scand.* **1955**, *9*, 383.
(141) Courtney, R. C.; Gustafson, R. L.; Westerback, S. J.; Hyytiainen, H.; Chaberek, S. C., Jr.; Martell, A. E. *J. Am. Chem. Soc.* **1957**, *79*, 3030.
(142) Epstein, J.; Rosenblatt, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 3596.
(143) Bamann, E.; Fischler, F.; Trapmann, H. *Biochem. Z.* **1954**, *325*, 413.
(144) Bamann, E.; Stadelmann, W.; Riehl, J. *Arch Pharm. Ber. Dtsch. Pharm. Ges.* **1959**, *292*, 36.
(145) Bamann, E.; Trapmann, H.; Fischler, F. *Biochem. Z.* **1954**, *326*, 89.
(146) Bamann, E.; Trapmann, H.; Krauss, H. J. *Arch. Pharm.* **1962**, *295*, 330.
(147) Bamann, E.; Trapmann, H.; Oechsner, B. *Arch. Pharm.* **1962**, *295*, 663.
(148) Epstein, J.; Mosher, W. A. *J. Phys. Chem.* **1968**, *72*, 622.
(149) Withey, R. J. *Can. J. Chem.* **1969**, *47*, 4383.
(150) Kenley, R. A.; Fleming, R. H.; Laine, R. M.; Tse, D. S.; Winterle, J. S. *Inorg. Chem.* **1984**, *23*, 1870.
(151) Ward, J. R.; Szafraniec, L. L.; Beaudry, W. T.; Hovanec, J. W. *J. Mol. Catal.* **1990**, *58*, 373.
(152) Brown, R. S.; Zamkanei, M. *Inorg. Chim. Acta* **1985**, *108*, 201.
(153) Norman, P. R.; Tate, A.; Rich, P. *Inorg. Chim. Acta* **1988**, *145*, 211.
(154) Hay, R. W.; Govan, N. *Transition Met. Chem.* **1998**, *23*, 133.
(155) Tafesse, F. *Inorg. Chim. Acta* **1998**, *269*, 287.
(156) Lewis, R. E.; Neverov, A. A.; Brown, R. S. *Org. Biomol. Chem.* **2005**, *3*, 4082.
(157) Hay, R. W.; Govan, N. *Polyhedron* **1998**, *17*, 2079.
(158) Hartshorn, C. M.; Singh, A.; Chang, E. L. *J. Mater. Chem.* **2002**, *12*, 602.
(159) Melnychuk, S. A.; Neverov, A. A.; Brown, R. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1767.

(160) Andrea, T.; Neverov, A. A.; Brown, R. S. *Ind. Eng. Chem. Res.* **2010**, *49*, 7027.
(161) Kuo, L. Y.; Adint, T. T.; Akagi, A. E.; Zakharov, L. *Organometallics* **2008**, *27*, 2560.
(162) Kuo, L. Y.; Blum, A. P.; Sabat, M. *Inorg. Chem.* **2005**, *44*, 5537.
(163) Kuo, L. Y.; Perera, N. M. *Inorg. Chem.* **2000**, *39*, 2103.
(164) Mitra, A.; Atwood, D. A.; Struss, J.; Williams, D. J.; McKinney, B. J.; Creasy, W. R.; McGarvey, D. J.; Durst, H. D.; Fry, R. *New J. Chem.* **2008**, *32*, 783.
(165) Uytingco, M. S.; Parida, S.; Wiencek, J. M.; Defrank, J. J. *Proc. ERDEC Sci. Conf. Chem. Biol. Def. Res.* **1996**, 343.
(166) Hay, R. W.; Govan, N. *Polyhedron* **1997**, *16*, 4233.
(167) Leslie, D. R.; Ward, J. R. Metal-ion catalyzed oxidation of a G agent simulant by ozone, Chem. Res. Dev. Eng. Cent., Aberdeen Proving Ground, MD, USA. FIELD URL, 1992.
(168) Hafiz, A. A. *J. Surfactants Deterg.* **2005**, *8*, 359.
(169) DeFrank, J. J. *Appl. Enzyme Biotechnol., [Proc. Tex. A&M Univ., IUCCP Symp.], 9th* **1991**, 165.
(170) Ternan, N. G.; Grath, J. W.; Mullan, G.; Quinn, J. P. *World J. Microbiol. Biotechnol.* **1998**, *14*, 635.
(171) Shell, T. A.; Mohler, D. L. *Curr. Org. Chem.* **2007**, *11*, 1525.
(172) Mancin, F.; Tecilla, P. *New J. Chem.* **2007**, *31*, 800.
(173) Waern, J. B.; Harding, M. M. *J. Organomet. Chem.* **2004**, *689*, 4655.
(174) Sreedhara, A.; Cowan, J. A. *J. Biol. Inorg. Chem.* **2001**, *6*, 337.
(175) Elashvili, I.; DeFrank, J. J.; Culotta, V. C. *Proc. ERDEC Sci. Conf. Chem. Biol. Def. Res.* 1999, 763.
(176) Mazur, A. *J. Biol. Chem.* **1946**, *164*, 271.
(177) Augustinsson, K. B. *Acta Chem. Scand.* **1957**, *11*, 1371.
(178) Augustinsson, K. B. *Acta Chem. Scand.* **1958**, *12*, 1286.
(179) Augustinsson, K. B.; Heimburger, G. *Acta Chem. Scand.* **1954**, *8*, 1533.
(180) Augustinsson, K. B.; Heimburger, G. *Acta Chem. Scand.* **1954**, *8*, 915.
(181) Augustinsson, K. B.; Heimburger, G. *Acta Chem. Scand.* **1954**, *8*, 762.
(182) Augustinsson, K. B.; Heimburger, G. *Acta Chem. Scand.* **1954**, *8*, 753.
(183) Augustinsson, K. B.; Heimburger, G. *Acta Chem. Scand.* **1955**, *9*, 310.
(184) Munnecke, D. M.; Hsieh, D. P. H. *Appl. Microbiol.* **1974**, *28*, 212.
(185) Munnecke, D. M.; Hsieh, D. P. H. *Appl. Microbiol.* **1975**, *30*, 575.
(186) Munnecke, D. M.; Hsieh, D. P. H. *Appl. Environ. Microbiol.* **1976**, *31*, 63.
(187) Munnecke, D. M. *Appl. Environ. Microbiol.* **1976**, *32*, 7.
(188) Munnecke, D. M. *Appl. Environ. Microbiol.* **1977**, *33*, 503.
(189) Cook, A. M.; Daughton, C. G.; Alexander, M. *Appl. Environ. Microbiol.* **1978**, *36*, 668.
(190) Cook, A. M.; Daughton, C. G.; Alexander, M. *J. Bacteriol.* **1978**, *133*, 85.
(191) La Nauze, J. M.; Rosenberg, H.; Shaw, D. C. *Biochim. Biophys. Acta, Enzymol.* **1970**, *212*, 332.
(192) Wackett, L. P.; Shames, S. L.; Venditti, C. P.; Walsh, C. T. *J. Bacteriol.* **1987**, *169*, 710.
(193) Attaway, H.; Nelson, J. O.; Baya, A. M.; Voll, M. J.; White, W. E.; Grimes, D. J.; Colwell, R. R. *Appl. Environ. Microbiol.* **1987**, *53*, 1685.
(194) Cordeiro, M. L.; Pompliano, D. L.; Frost, J. W. *J. Am. Chem. Soc.* **1986**, *108*, 332.
(195) Avila, L. Z.; Loo, S. H.; Frost, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 6758.
(196) Avila, L. Z.; Draths, K. M.; Frost, J. W. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 51.
(197) Gilbert, E. S.; Walker, A. W.; Keasling, J. D. *Appl. Microbiol. Biotechnol.* **2003**, *61*, 77.
(198) Wang, A. A.; Chen, W.; Mulchandani, A. *Biotechnol. Bioeng.* **2005**, *91*, 379.
(199) McLoughlin, S. Y.; Jackson, C.; Liu, J.-W.; Ollis, D. L. *Appl. Environ. Microbiol.* **2004**, *70*, 404.
(200) Daughton, C. G.; Cook, A. M.; Alexander, M. *J. Agric. Food Chem.* **1979**, *27*, 1375.
(201) Cook, A. M.; Daughton, C. G.; Alexander, M. *Appl. Environ. Microbiol.* **1980**, *39*, 463.
(202) Serdar, C. M.; Gibson, D. T.; Munnecke, D. M.; Lancaster, J. H. *Appl. Environ. Microbiol.* **1982**, *44*, 246.
(203) Zboinska, E.; Lejczak, B.; Kafarski, P. *Appl. Environ. Microbiol.* **1992**, *58*, 2993.
(204) Walker, A. W.; Keasling, J. D. *Biotechnol. Bioeng.* **2002**, *78*, 715.
(205) Lei, Y.; Mulchandani, A.; Chen, W. *Biotechnol. Prog.* **2005**, *21*, 678.
(206) Kulkarni, M.; Chaudhari, A. *Bioresour. Technol.* **2006**, *97*, 982.
(207) Mattozzi, M. D. P.; Tehara, S. K.; Hong, T.; Keasling, J. D. *Appl. Environ. Microbiol.* **2006**, *72*, 6699.
(208) DeFrank, J. J.; Cheng, T. C. *J. Bacteriol.* **1991**, *173*, 1938.
(209) Harvey, S. P.; Kolakowski, J. E.; Cheng, T.-C.; Rastogi, V. K.; Reiff, L. P.; DeFrank, J. J.; Raushel, F. M.; Hill, C. *Enzyme Microb. Technol.* **2005**, *37*, 547.
(210) Cheng, T.-C.; Calomiris, J. J. *Enzyme Microb. Technol.* **1996**, *18*, 597.
(211) Cho, C. M. H.; Mulchandani, A.; Chen, W. *Appl. Environ. Microbiol.* **2002**, *68*, 2026.
(212) diSioudi, B.; Grimsley, J. K.; Lai, K. H.; Wild, J. R. *Biochemistry* **1999**, *38*, 2866.
(213) Gordon, R. K.; Feaster, S. R.; Russell, A. J.; LeJeune, K. E.; Maxwell, D. M.; Lenz, D. E.; Ross, M.; Doctor, B. P. *Chem.-Biol. Interact.* **1999**, *119−120*, 463.
(214) Gill, I.; Ballesteros, A. *Biotechnol. Bioeng.* **2000**, *70*, 400.
(215) Mansee, A. H.; Chen, W.; Mulchandani, A. *J. Ind. Microbiol. Biotechnol.* **2005**, *32*, 554.
(216) Lenz, D. E.; Yeung, D.; Smith, J. R.; Sweeney, R. E.; Lumley, L. A.; Cerasoli, D. M. *Toxicology* **2007**, *233*, 31.
(217) Brimfield, A. A.; Hunter, K. W., Jr.; Lenz, D. E.; Benschop, H. P.; Van Dijk, C.; De Jong, L. P. A. *Mol. Pharmacol.* **1985**, *28*, 32.
(218) Benschop, H. P.; Berends, F.; De Jong, L. P. A. *Fundam. Appl. Toxicol.* **1981**, *1*, 177.
(219) Benschop, H. P.; Konings, C. A. G.; De Jong, L. P. A. *J. Am. Chem. Soc.* **1981**, *103*, 4260.
(220) Gramstad, T.; Fuglevik, W. J. *Acta Chem. Scand.* **1962**, *16*, 2368.
(221) Ngeh-Ngwainbi, J.; Foley, P. H.; Kuan, S. S.; Guilbault, G. G. *J. Am. Chem. Soc.* **1986**, *108*, 5444.
(222) Buenafe, A. C.; Rittenberg, M. B. *Mol. Immunol.* **1987**, *24*, 401.
(223) Erhard, M. H.; Schmidt, P.; Kuehlmann, R.; Loesch, U. *Arch. Toxicol.* **1989**, *63*, 462.
(224) Erhard, M. H.; Kuehlmann, R.; Szinicz, L.; Loesch, U. *Arch. Toxicol.* **1990**, *64*, 580.
(225) Lenz, D. E.; Yourick, J. J.; Dawson, J. S.; Scott, J. *Immunol. Lett.* **1992**, *31*, 131.
(226) Glikson, M.; Aradyellin, R.; Ghozi, M.; Raveh, L.; Green, B. S.; Eshhar, Z. *Mol. Immunol.* **1992**, *29*, 903.
(227) Erhard, M. H.; Jungling, A.; Schoneberg, T.; Szinicz, L.; Losch, U. *Arch. Toxicol.* **1993**, *67*, 220.
(228) Grognet, J. M.; Ardouin, T.; Istin, M.; Vandais, A.; Noel, J. P.; Rima, G.; Satge, J.; Pradel, C.; Sentenacroumanou, H.; Lion, C. *Arch. Toxicol.* **1993**, *67*, 66.
(229) Ashani, Y.; Radic, Z.; Tsigelny, I.; Vellom, D. C.; Pickering, N. A.; Quinn, D. M.; Doctor, B. P.; Taylor, P. *J. Biol. Chem.* **1995**, *270*, 6370.
(230) Wilson, I. B.; Froede, H. C. *Med. Chem., Ser. Monogr.* **1971**, *11*, 213.
(231) Kitz, R. J.; Ginsburg, S.; Wilson, I. B. *Biochem. Pharmacol.* **1965**, *14*, 1471.
(232) Wong, L.; Radic, Z.; Brueggemann, R. J. M.; Hosea, N.; Berman, H. A.; Taylor, P. *Biochemistry* **2000**, *39*, 5750.
(233) Yli-Kauhaluoma, J.; Humppi, T.; Yliniemela, A. *Acta Chem. Scand.* **1999**, *53*, 473.

(234) Brimfield, A. A.; Lenz, D. E.; Maxwell, D. M.; Broomfield, C. A. *Chem.-Biol. Interact.* **1993**, *87*, 95.
(235) Vayron, P.; Renard, P. Y.; Valleix, A.; Mioskowski, C. *Chem.—Eur. J.* **2000**, *6*, 1050.
(236) Kovarik, Z.; Radic, Z.; Berman, H. A.; Simeon-Rudolf, V.; Reiner, E.; Taylor, P. *Biochemistry* **2004**, *43*, 3222.
(237) Doctor, B. P.; Saxena, A. *Chem.-Biol. Interact.* **2005**, *157—158*, 167.
(238) Johnson, J. K.; Cerasoli, D. M.; Lenz, D. E. *Immunol. Lett.* **2005**, *96*, 121.
(239) Kovarik, Z.; Radic, Z.; Berman, H. A.; Taylor, P. *Toxicology* **2007**, *233*, 79.
(240) Huang, Y. J.; Huang, Y.; Baldassarre, H.; Wang, B.; Lazaris, A.; Leduc, M.; Bilodeau, A. S.; Bellemare, A.; Cote, M.; Herskovits, P.; Touati, M.; Turcotte, C.; Valeanu, L.; Lemee, N.; Wilgus, H.; Begin, I.; Bhatia, B.; Rao, K.; Neveu, N.; Brochu, E.; Pierson, J.; Hockley, D. K.; Cerasoli, D. M.; Lenz, D. E.; Karatzas, C. N.; Langermann, S. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13603.
(241) Saxena, A.; Sun, W.; Dabisch, P. A.; Hulet, S. W.; Hastings, N. B.; Jakubowski, E. M.; Mioduszewski, R. J.; Doctor, B. P. *Chem.-Biol. Interact.* **2008**, *175*, 267.
(242) Raushel, F. M. *Curr. Opin. Microbiol.* **2002**, *5*, 288.
(243) Lewis, V. E.; Donarski, W. J.; Wild, J. R.; Raushel, F. M. *Biochemistry* **1988**, *27*, 1591.
(244) Donarski, W. J.; Dumas, D. P.; Heitmeyer, D. P.; Lewis, V. E.; Raushel, F. M. *Biochemistry* **1989**, *28*, 4650.
(245) Dumas, D. P.; Caldwell, S. R.; Wild, J. R.; Raushel, F. M. *J. Biol. Chem.* **1989**, *264*, 19659.
(246) Caldwell, S. R.; Newcomb, J. R.; Schlecht, K. A.; Raushel, F. M. *Biochemistry* **1991**, *30*, 7438.
(247) Caldwell, S. R.; Raushel, F. M.; Weiss, P. M.; Cleland, W. W. *Biochemistry* **1991**, *30*, 7444.
(248) Blankenship, J. N.; Abu-Soud, H.; Francisco, W. A.; Raushel, F. M.; Fischer, D. R.; Stang, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8560.
(249) Omburo, G. A.; Kuo, J. M.; Mullins, L. S.; Raushel, F. M. *J. Biol. Chem.* **1992**, *267*, 13278.
(250) Kuo, J. M.; Chae, M. Y.; Raushel, F. M. *Biochemistry* **1997**, *36*, 1982.
(251) Hong, S.-B.; Mullins, L. S.; Shim, H.; Raushel, F. M. *Biochemistry* **1997**, *36*, 9022.
(252) Hong, S.-B.; Raushel, F. M. *Biochemistry* **1999**, *38*, 1159.
(253) Chen-Goodspeed, M.; Sogorb, M. A.; Wu, F.; Hong, S.-B.; Raushel, F. M. *Biochemistry* **2001**, *40*, 1325.
(254) Chen-Goodspeed, M.; Sogorb, M. A.; Wu, F.; Raushel, F. M. *Biochemistry* **2001**, *40*, 1332.
(255) Anderson, M. A.; Shim, H.; Raushel, F. M.; Cleland, W. W. *J. Am. Chem. Soc.* **2001**, *123*, 9246.
(256) Hill, C. M.; Li, W.-S.; Thoden, J. B.; Holden, H. M.; Raushel, F. M. *J. Am. Chem. Soc.* **2003**, *125*, 8990.
(257) *Caution*: hydrolyzed or modified derivatives may still retain toxicity.
(258) Soares, T. A.; Osman, M. A.; Straatsma, T. P. *J. Chem. Theory Comput.* **2007**, *3*, 1569.
(259) Li, Y.; Aubert, S. D.; Raushel, F. M. *J. Am. Chem. Soc.* **2003**, *125*, 7526.
(260) Tsai, P. C.; Bigley, A.; Li, Y. C.; Ghanem, E.; Cadieux, C. L.; Kasten, S. A.; Reeves, T. E.; Cerasoli, D. M.; Raushel, F. M. *Biochemistry* **2010**, *49*, 7978.
(261) Aubert, S. D.; Li, Y.; Raushel, F. M. *Biochemistry* **2004**, *43*, 5707.
(262) Rochu, D.; Viguie, N.; Renault, F.; Crouzier, D.; Froment, M.-T.; Masson, P. *Biochem. J.* **2004**, *380*, 627.
(263) Briseno-Roa, L.; Hill, J.; Notman, S.; Sellers, D.; Smith, A. P.; Timperley, C. M.; Wetherell, J.; Williams, N. H.; Williams, G. R.; Fersht, A. R.; Griffiths, A. D. *J. Med. Chem.* **2006**, *49*, 246.
(264) Ghanem, E.; Li, Y. C.; Xu, C. F.; Raushel, F. M. *Biochemistry* **2007**, *46*, 9032.
(265) Wong, K.-Y.; Gao, J. *Biochemistry* **2007**, *46*, 13352.
(266) Tsai, P. C.; Fan, Y. B.; Kim, J.; Yang, L. J.; Almo, S. C.; Gao, Y. Q.; Raushel, F. M. *Biochemistry* **2010**, *49*, 7988.
(267) Dyguda-Kazimierowicz, E.; Sokalski, W. A.; Leszczynski, J. *J. Phys. Chem. B* **2008**, *112*, 9982.
(268) Sussman, J. L.; Harel, M.; Frolow, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. *Science* **1991**, *253*, 872.
(269) Hemmert, A. C.; Otto, T. C.; Wierdl, M.; Edwards, C. C.; Fleming, C. D.; MacDonald, M.; Cashman, J. R.; Potter, P. M.; Cerasoli, D. M.; Redinbo, M. R. *Mol. Pharmacol.* **2010**, *77*, 508.
(270) Hosea, N. A.; Berman, H. A.; Taylor, P. *Biochemistry* **1995**, *34*, 11528.
(271) Berman, H. A.; Leonard, K. *J. Biol. Chem.* **1989**, *264*, 3942.
(272) Berman, H. A.; Decker, M. M. *J. Biol. Chem.* **1989**, *264*, 3951.
(273) Sogorb, M. A.; Garcia-Arguelles, S.; Carrera, V.; Vilanova, E. *Chem. Res. Toxicol.* **2008**, *21*, 1524.
(274) Li, B.; Nachon, F.; Froment, M.-T.; Verdier, L.; Debouzy, J.-C.; Brasme, B.; Gillon, E.; Schopfer, L. M.; Lockridge, O.; Masson, P. *Chem. Res. Toxicol.* **2008**, *21*, 421.
(275) Harel, M.; Aharoni, A.; Gaidukov, L.; Brumshtein, B.; Khersonsky, O.; Meged, R.; Dvir, H.; Ravelli, R. B. G.; McCarthy, A.; Toker, L.; Silman, I.; Sussman, J. L.; Tawfik, D. S. *Nat. Struct. Mol. Biol.* **2004**, *11*, 412.
(276) Dave, K. I.; Phillips, L.; Luckow, V. A.; Wild, J. R. *Biotechnol. Appl. Biochem.* **1994**, *19*, 271.
(277) Mounter, L. A.; Floyd, C. S.; Chanutin, A. *J. Biol. Chem.* **1953**, *204*, 221.
(278) Hoskin, F. C. G.; Roush, A. H. *Science* **1982**, *215*, 1255.
(279) Gab, J.; Melzer, M.; Kehe, K.; Richardt, A.; Blum, M.-M. *Anal. Biochem.* **2009**, *385*, 187.
(280) Bruno, J. G.; Carrillo, M. P.; Cadieux, C. L.; Lenz, D. E.; Cerasoli, D. M.; Phillips, T. *J. Mol. Recognit.* **2009**, *22*, 197.
(281) Van Hooidonk, C.; Breebaart-Hansen, J. C. A. E. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 289.
(282) Desire, B.; Saint-Andre, S. *Experientia* **1987**, *43*, 395.
(283) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997.
(284) Barr, L.; Easton, C. J.; Lee, K.; Lincoln, S. F.; Simpson, J. S. *Tetrahedron Lett.* **2002**, *43*, 7797.
(285) Hoskin, F. C.; Steeves, D. M.; Walker, J. E. *Biol. Bull.* **1999**, *197*, 284.
(286) Masurier, N.; Estour, F.; Froment, M.-T.; Lefevre, B.; Debouzy, J.-C.; Brasme, B.; Masson, P.; Lafont, O. *Eur. J. Med. Chem.* **2005**, *40*, 615.
(287) Wille, T.; Tenberken, O.; Reiter, G.; Mueller, S.; Le Provost, R.; Lafont, O.; Estour, F.; Thiermann, H.; Worek, F. *Toxicology* **2009**, *265*, 96.
(288) Wille, T.; Thiermann, H.; Worek, F. *Toxicol. In Vitro* **2010**, *24*, 1026.
(289) Simanenko, Y. S.; Savelova, V. A.; Prokop'eva, T. M.; Mikhailov, V. A.; Turovskaya, M. K.; Karpichev, E. A.; Popov, A. F.; Gillitt, N. D.; Bunton, C. A. *J. Org. Chem.* **2004**, *69*, 9238.
(290) Simanenko, Y. S.; Popov, A. F.; Prokop'eva, T. M.; Karpichev, E. A.; Savelova, V. A.; Suprun, I. P.; Bunton, C. A. *Russ. J. Org. Chem.* **2002**, *38*, 1341.
(291) Gershonov, E.; Columbus, I.; Zafrani, Y. *J. Org. Chem.* **2009**, *74*, 329.
(292) Spafford, R. B. The Development of a Reactive Sorbent for Immediate Decontamination, ERDEC-CR-218, 1996.
(293) Wagner, G. W.; Bartram, P. W. *Langmuir* **1999**, *15*, 8113.
(294) Keizer, T. S.; De Pue, L. J.; Parkin, S.; Atwood, D. A. *J. Am. Chem. Soc.* **2002**, *124*, 1864.
(295) Butala, R. R.; Cooper, J. K.; Mitra, A.; Webster, M. K.; Atwood, D. A. *Main Group Chem.* **2010**, *9*, 315.
(296) Smentkowski, V. S.; Hagans, P.; Yates, J. T. *J. Phys. Chem.* **1988**, *92*, 6351.
(297) Hegde, R. I.; Greenlief, C. M.; White, J. M. *J. Phys. Chem.* **1985**, *89*, 2886.
(298) Guo, X.; Yoshinobu, J.; Yates, J. T. *J. Phys. Chem.* **1990**, *94*, 6839.
(299) Henderson, M. A.; White, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 6939.

(300) Dulcey, C. S.; Lin, M. C.; Hsu, C. C. *Chem. Phys. Lett.* **1985**, *115*, 481.
(301) Gordon, W. O.; Tissue, B. M.; Morris, J. R. *J. Phys. Chem. C* **2007**, *111*, 3233.
(302) Hedge, R. I.; White, J. M. *Appl. Surf. Sci.* **1987**, *28*, 1.
(303) Templeton, M. K.; Weinberg, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 97.
(304) Henderson, M. A.; Jin, T.; White, J. M. *J. Phys. Chem.* **1986**, *90*, 4607.
(305) Cardenastrivino, G.; Klabunde, K. J. *Bol. Soc. Chil. Quim.* **1988**, *33*, 163.
(306) Li, Y. X.; Klabunde, K. J. *Langmuir* **1991**, *7*, 1388.
(307) Li, Y. X.; Schlup, J. R.; Klabunde, K. J. *Langmuir* **1991**, *7*, 1394.
(308) Rajagopalan, S.; Koper, O.; Decker, S.; Klabunde, K. J. *Chem.—Eur. J.* **2002**, *8*, 2602.
(309) Medine, G. M.; Zaikovskii, V.; Klabunde, K. J. *J. Mater. Chem.* **2004**, *14*, 757.
(310) Wagner, G. W.; Bartram, P. W.; Koper, O.; Klabunde, K. J. *J. Phys. Chem. B* **1999**, *103*, 3225.
(311) Nazari, B.; Jaafari, M. *Dig. J. Nanomater. Biostruct.* **2010**, *5*, 909.
(312) Decker, S. P.; Klabunde, J. S.; Khaleel, A.; Klabunde, K. J. *Environ. Sci. Technol.* **2002**, *36*, 762.
(313) Wagner, G. W.; Koper, O. B.; Lucas, E.; Decker, S.; Klabunde, K. J. *J. Phys. Chem. B* **2000**, *104*, 5118.
(314) Wagner, G. W.; Procell, L. R.; O'Connor, R. J.; Munavalli, S.; Carnes, C. L.; Kapoor, P. N.; Klabunde, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 1636.
(315) Bermudez, V. M. *J. Phys. Chem. C* **2009**, *113*, 1917.
(316) Saxena, A.; Srivastava, A. K.; Singh, B.; Gupta, A. K.; Suryanarayana, M. V. S.; Pandey, P. *J. Hazard. Mater.* **2010**, *175*, 795.
(317) Kolodziejczyk, W.; Majuradar, D.; Roszak, S.; Leszczynski, J. *Chem. Phys. Lett.* **2007**, *450*, 138.
(318) Michalkova, A.; Gorb, L.; Ilchenko, M.; Zhikol, O. A.; Shishkin, O. V.; Leszczynski, J. *J. Phys. Chem. B* **2004**, 1918.
(319) For related computational studies, see the recent book chapter by J. Leszczynski et al. entitled, "A quest for efficient methods of disintegration of organophosphorus compounds: modeling adsorption and decomposition processes." See next reference.
(320) Michalkova, A.; Gorb, L.; Leszczynski, J. *Molecular Materials with Specific Interactions*; Springer, 2007.
(321) Kanan, S. M.; Tripp, C. P. *Langmuir* **2002**, *18*, 722.
(322) Quenneville, J.; Taylor, R. S.; van Duin, A. C. T. *J. Phys. Chem. C* **2010**, *114*, 18894.
(323) Kanan, S. M.; Tripp, C. P. *Langmuir* **2001**, *17*, 2213.
(324) Kim, C. S.; Lad, R. J.; Tripp, C. P. *Sens. Actuators, B* **2001**, *B76*, 442.
(325) Kozlova, E. A.; Vorontsov, A. V. *Appl. Catal., B* **2006**, *63*, 114.
(326) Zhou, J.; Varazo, K.; Reddic, J. E.; Myrick, M. L.; Chen, D. A. *Anal. Chim. Acta* **2003**, *496*, 289.
(327) Sharabi, D.; Paz, Y. *Appl. Catal., B* **2010**, *95*, 169.
(328) Mera, N.; Hirakawa, T.; Sano, T.; Takeuchi, K.; Seto, Y.; Negishi, N. *J. Hazard. Mater.* **2010**, *177*, 274.
(329) Alvaro, M.; Cojocaru, B.; Ismail, A. A.; Petrea, N.; Ferrer, B.; Harraz, F. A.; Parvulescu, V. I.; Garcia, H. *Appl. Catal., B* **2010**, *99*, 191.
(330) Neatu, S.; Cojocaru, B.; Parvulescu, V. I.; Somoghi, V.; Alvaro, M.; Garcia, H. *J. Mater. Chem.* **2010**, *20*, 4050.
(331) Hirakawa, T.; Sato, K.; Komano, A.; Kishi, S.; Nishimoto, C. K.; Mera, N.; Kugishima, M.; Sano, T.; Ichinose, H.; Negishi, N.; Seto, Y.; Takeuchi, K. *J. Phys. Chem. C* **2010**, *114*, 2305.
(332) Kanan, S. M.; Lu, Z.; Tripp, C. P. *J. Phys. Chem. B* **2002**, *106*, 9576.
(333) Lu, Z. X.; Kanan, S. M.; Tripp, C. P. *J. Mater. Chem.* **2002**, *12*, 983.
(334) Kanan, S. M.; Waghe, A.; Jensen, B. L.; Tripp, C. P. *Talanta* **2007**, *72*, 401.
(335) Mahato, T. H.; Prasad, G. K.; Singh, B.; Batra, K.; Ganesan, K. *Microporous Mesoporous Mater.* **2010**, *132*, 15.
(336) Stengl, V.; Houskova, V.; Bakardjieva, S.; Murafa, N.; Marikova, M.; Oplustil, F.; Nemec, T. *Mater. Charact.* **2010**, *61*, 1080.
(337) Taranenko, N.; Alarie, J.-P.; Stokes, D. L.; Dinh, T.-V. *J. Raman Spectrosc.* **1996**, *27*, 379.
(338) DeBurgomaster, P.; Ouellette, W.; Liu, H.; O'Connor, C. J.; Zubieta, J. *CrystEngComm* **2010**, *12*, 446.
(339) Zhao, Q.; Zhu, Q.; Shih, W. Y.; Shih, W.-H. *Sens. Actuators, B* **2006**, *B117*, 74.
(340) Hartzell, C. J.; Yang, S.-W.; Parnell, R. A.; Morris, D. E. *J. Phys. Chem. A* **1995**, *99*, 4205.
(341) Jang, M. S.; Lee, S. J.; Xue, X.; Kwon, H.-M.; Ra, C. S.; Lee, Y. T.; Chung, T. *Bull. Korean Chem. Soc.* **2002**, *23*, 1116.
(342) Jang, S. H.; Koh, Y. D.; Kim, J. H.; Sohn, H. L. *J. Korean Phys. Soc.* **2008**, *52*, 212.
(343) Ruminski, A. M.; Moore, M. M.; Sailor, M. J. *Adv. Funct. Mater.* **2008**, *18*, 3418.
(344) Beaudry, W. T.; Wagner, G. W.; Ward, J. R. *J. Mol. Catal.* **1992**, *73*, 77.
(345) Xie, H. F.; Yang, Q. D.; Sun, X. X.; Yu, T.; Zhou, J.; Huang, Y. P. *Sens. Mater.* **2005**, *17*, 21.
(346) Knagge, K.; Johnson, M.; Grassian, V. H.; Larsen, S. C. *Langmuir* **2006**, *22*, 11077.
(347) Williamson, C. J.; O'Brien, P. *J. Mater. Chem.* **1994**, *4*, 565.
(348) Nistiar, F.; Mojzis, J.; Kovac, G.; Seidel, H.; Racz, O. *Folia Microbiol.* **2000**, *45*, 567.
(349) Yang, S. W.; Doetschman, D. C.; Schulte, J. T.; Sarnbur, J. B.; Kanyi, C. W.; Fox, J. D. *Microporous Mesoporous Mater.* **2006**, *92*, 56.
(350) Mojzis, J.; Nistiar, F.; Kovac, G.; Mojzisova, G. *Vet. Med.* **1994**, *39*, 443.
(351) Kovac, G.; Reichel, P.; Seidel, H.; Mudron, P. *Czech. J. Anim. Sci.* **1998**, *43*, 3.
(352) Moss, J. A.; Szczepankiewicz, S. H.; Park, E.; Hoffmann, M. R. *J. Phys. Chem. B* **2005**, *109*, 19779.
(353) Ashani, Y.; Bromberg, A.; Levy, D.; Gentry, M. K.; Brady, D. R.; Doctor, B. P. *Cholinesterases Proc. Int. Meet. Cholinesterases, 3rd* **1991**, 235.
(354) Herrmann, H. W.; Selwyn, G. S.; Henins, I.; Park, J.; Jeffery, M.; Williams, J. M. *IEEE Trans. Plasma Sci.* **2002**, *30*, 1460.
(355) Xie, Y. W.; Popov, B. N.; White, R. E. *J. Electroanal. Chem.* **1999**, *466*, 169.
(356) Abel, A. E.; Mouk, R. W.; Heyduk, A. F.; Blum, B. J.; Getman, G. D.; Steskal, M. D.Method and apparatus to destroy chemical warfare agents. WO Patent 9718858, October 10, 1996.
(357) Prasad, G. K.; Singh, B.; Mahato, T. H.; Pandey, K. S.; Ganesan, K.; Acharya, J.; Vijayaraghavan, R. An organic formulation for decontamination of chemical agents. IN Patent 2397/DEL/2007, November 14, 2007.
(358) Puckett, P. M.; Livesay, M.; Clement, K. S. Compositions for neutralization and decontamination of toxic chemical and biological agents. WO Patent 09/023731, August 13, 2008.
(359) Chabriere, E.; Elias, M. Variants of phosphotriesterases of hyperthermophilic microorganisms and their use in degradation of organophosphates in poisoning or contamination. WO Patent 08/145865, April 25, 2008.
(360) Wagner, G. W. Activated peroxide solution with improved stability useful for the decontamination of chemical warfare agents. U.S. Patent 7,442,677, August 24, 2005.
(361) Ramakrishna, S.; Subramanian, S. Fibers for decontamination of chemical and biological agents. WO Patent 08/127200, April 11, 2008.
(362) Kaiser, H. J.; Thanavaro, A.; Dell'aringa, B. W.; Tienes, B. M.; Klein, D. A.; Wagner, G. W. One part, solids containing decontamination blend composition. U.S. Patent 08/0045593, July 24, 2007.
(363) Blum, M.-M.; Richardt, A. *Decontam. Warf. Agents* **2008**, 135.
(364) Robertson, D. E.; Richardson, T.; Kustedjo, K.; Amitai, G.; LeJeune, K.; Berberich, J.; Chaplin, J. A.; Sinclair, J. Enzymes and formulations for broad-specificity decontamination of chemical and biological warfare agents. WO Patent 08/036061, April 6, 2006.
(365) Cheng, T.-C.; DeFrank, J. J.; Harvey, S. P.; Rastogi, V. K. Enzyme-based non-corrosive, non-caustic, and non-flammable decontaminant formulations for organophosphorus compounds. U.S. Patent 7,229,819, October 27, 2003.

(366) Lee, Y.; Riecker, A.; Mendum, T.; Puglia, J. P. *Abstr. Pap., ACS Natl. Meet.* **2007**, *233*, No. CELL.
(367) Brown, J. S. Chemical and biological warfare decontaminating solution using bleach activators. U.S. Patent 03/0045767, February 1, 2002.
(368) Wagner, G. W.; Yang, Y. C. Universal decontaminating solution for chemical warfare agents. U.S. Patent 6,245,957, September 2, 1999.
(369) Wartell, M. A.; Kleinman, M. T.; Huey, B. M.; Duffy, L. M.; NRC *Strategies to Protect the Health of Deployed U.S. Forces: Force Protection and Decontamination*; National Academies Press: Washington, D.C., 1999.
(370) Fatah, A. A.; Barrett, J. A.; Richard, D. Arcilesi, J.; Ewing, D. K. J.; Lattin, C. H.; Helinski, M. S.; Baig, I. A. Guide for the Selection of Chemical and Biological Decontamination Equipment for Emergency First Responders NIJ Guide 103−00 Vol. I, National Institute of Standards and Technology (NIST), October 2001.
(371) Bannard, R. A. B.; Casselman, A. A.; Purdon, J. G.; Bovenkamp, J. W. Broad spectrum chemical decontaminant system. U.S. Patent 5,075,297, November 20, 1984.
(372) Bannard, R. A. B.; Casselman, A. A.; Purdon, J. G.; Mendoza, C. E. Chemical warfare agent decontaminant composition containing an alkali metal salt of oximes, phenols, or PEG monoethers. GB Patent 2,239,598, March 19, 1987.
(373) Tan, H. Y.; Loke, W. K.; Tan, Y. T.; Nguyen, N. T. *Lab Chip* **2008**, *8*, 885.
(374) Khalil, S.; Bansal, L.; El-Sherif, M. *Opt. Eng.* **2004**, *43*, 2683.
(375) Green, M. L. H. *J. Organomet. Chem.* **1995**, *500*, 127.
(376) Wiener, S. W.; Hoffman, R. S. *J. Intensive Care Med.* **2004**, *19*, 22.
(377) Endregard, M.; Reif, B. A. P.; Vik, T.; Busmundrud, O. *J. Hazard. Mater.* **2010**, *176*, 381.
(378) Karlsson, E. *J. Hazard. Mater.* **1994**, *38*, 313.
(379) Karlsson, E.; Huber, U. *J. Hazard. Mater.* **1996**, *49*, 15.
(380) Ward, J. R.; Hovanec, J. W.; Albizo, J. M.; Szafraniec, L. L.; Beaudry, W. T. *J. Fluorine Chem.* **1991**, *51*, 277.
(381) Singer, B. C.; Hodgson, A. T.; Destaillats, H.; Hotchi, T.; Revzan, K. L.; Sextro, R. G. *Environ. Sci. Technol.* **2005**, *39*, 3203.
(382) Groenewold, G. S.; Williams, J. M.; Appelhans, A. D.; Gresham, G. L.; Olson, J. E.; Jeffery, M. T.; Rowland, B. *Environ. Sci. Technol.* **2002**, *36*, 4790.
(383) Williams, J. M.; Rowland, B.; Jeffery, M. T.; Groenewold, G. S.; Appelhans, A. D.; Gresham, G. L.; Olson, J. E. *Langmuir* **2005**, *21*, 2386.
(384) Wagner, G. W.; O'Connor, R. J.; Edwards, J. L.; Brevett, C. A. S. *Langmuir* **2004**, *20*, 7146.
(385) Gura, S.; Tzanani, N.; Hershkovitz, M.; Barak, R.; Dagan, S. *Arch. Environ. Contam. Toxicol.* **2006**, *51*, 1.
(386) Love, A. H.; Vance, A. L.; Reynolds, J. G.; Davisson, M. L. *Chemosphere* **2004**, *57*, 1257.
(387) Dannenberg, A.; Pehkonen, S. O. *J. Agric. Food Chem.* **1998**, *46*, 325.
(388) Jenkins, R. A.; Buchanan, M. V.; Merriweather, R.; Ilgner, R. H.; Gayle, T. M.; Watson, A. P. *J. Hazard. Mater.* **1994**, *37*, 303.
(389) Epstein, J. *Science* **1970**, *170*, 1396.
(390) Kingery, A. F.; Allen, H. E. *Toxicol. Environ. Chem.* **1995**, *47*, 155.
(391) Khordagui, H. *Mar. Environ. Res.* **1996**, *41*, 133.
(392) Khordagui, H. K. *Environ. Int.* **1995**, *21*, 363.
(393) Glasby, G. P. *Sci. Total Environ.* **1997**, *206*, 267.
(394) Kingery, A. F.; Saxe, J. K.; Allen, H. E. *Abstr., ACS Natl. Meet.* 2000, *219*, No. ENVR.
(395) D'Agostino, P. A.; Provost, L. R. *J. Chromatogr.* **1992**, *589*, 287.
(396) D'Agostino, P. A.; Provost, L. R.; Looye, K. M. *J. Chromatogr.* **1989**, *465*, 271.
(397) Montauban, C.; Begos, A.; Bellier, B. *Anal. Chem.* **2004**, *76*, 2791.
(398) Lowry, M. I.; Bartelt-Hunt, S. L.; Beaulieu, S. M.; Barlaz, M. A. *Environ. Sci. Technol.* **2008**, *42*, 7444.
(399) Bartelt-Hunt, S. L.; Barlaz, M. A.; Knappe, D. R. U.; Kjeldsen, P. *Environ. Sci. Technol.* **2006**, *40*, 4219.
(400) Bannister, E.; Cotton, F. A. *J. Chem. Soc.* **1960**, 2276.
(401) Cotton, F. A.; Goodgame, D. M. L. *J. Am. Chem. Soc.* **1960**, *82*, 5771.
(402) Guilbault, G. G.; Herrin, C. *Anal. Chim. Acta* **1967**, *37*, 412.
(403) Sheldon, J. C.; Tyree, S. Y. *J. Am. Chem. Soc.* **1958**, *80*, 4775.
(404) Goodgame, D. M. L.; Cotton, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 5774.
(405) Cotton, F. A.; Barnes, R. D.; Bannister, E. *J. Chem. Soc.* **1960**, 2199.
(406) Goodgame, D. M. L.; Cotton, F. A. *J. Chem. Soc.* **1961**, 2298.
(407) Berlin, K. D.; Pagilagan, R. U. *Chem. Commun.* **1966**, 687.
(408) Tschinkl, M.; Bachman, R. E.; Gabbai, F. P. *Organometallics* **2000**, *19*, 2633.
(409) Errington, R. J.; Ridland, J.; Willett, K. J.; Clegg, W.; Coxall, R. A.; Heath, S. L. *J. Organomet. Chem.* **1998**, *550*, 473.
(410) Bandyopadhyay, I.; Kim, M. J.; Lee, Y. S.; Churchill, D. G. *J. Phys. Chem. A* **2006**, *110*, 3655.
(411) Mao, J.-G. *Coord. Chem. Rev.* **2007**, *251*, 1493.
(412) Comba, P.; Gloe, K.; Inoue, K.; Kruger, T.; Stephan, H.; Yoshizuka, K. *Inorg. Chem.* **1998**, *37*, 3310.
(413) Gramstad, T. *Acta Chem. Scand.* **1961**, *15*, 1337.
(414) Aksnes, G.; Gramstad, T. *Acta Chem. Scand.* **1960**, *14*, 1485.
(415) Gramstad, T.; Snaprud, S. I. *Acta Chem. Scand.* **1962**, *16*, 999.
(416) Burke, R. W.; Yoe, J. H. *Talanta* **1963**, *10*, 1267.
(417) Jain, P. C.; Nigam, H. L. *Indian J. Chem.* **1970**, *8*, 456.
(418) Casals, I.; Gonzalez-Duarte, P.; Lopez, C.; Solans, X. *Polyhedron* **1990**, *9*, 763.
(419) Jones, C.; Lee, F. C.; Koutsantonis, G. A.; Gardiner, M. G.; Raston, C. L. *J. Chem. Soc., Dalton Trans.* **1996**, 829.
(420) Briand, G. G.; Burford, N.; Cameron, T. S.; Kwiatkowski, W. *J. Am. Chem. Soc.* **1998**, *120*, 11374.
(421) McMahon, C. N.; Francis, J. A.; Bott, S. G.; Barron, A. R. *J. Chem. Soc., Dalton Trans.* **1999**, 67.
(422) Bouziotis, P.; Papagiannopoulou, D.; Pirmettis, I.; Pelecanou, M.; Raptopoulou, C. P.; Stassinopoulou, C. I.; Terzis, A.; Friebe, M.; Spies, H.; Papadopoulos, M.; Chiotellis, E. *Inorg. Chim. Acta* **2001**, *320*, 174.
(423) Bouziotis, P.; Pirmettis, I.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Papadopoulos, M.; Chiotellis, E. *Chem.—Eur. J.* **2001**, *7*, 3671.
(424) Dey, S.; Jain, V. K.; Knoedler, A.; Kaim, W. *Indian J. Chem., Sect A* **2003**, *42A*, 2339.
(425) Mikuriya, M.; Okawa, H.; Kida, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2871.
(426) Mikuriya, M.; Okawa, H.; Kida, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1086.
(427) Mikuriya, M.; Toriumi, K.; Ito, T.; Kida, S. *Inorg. Chem.* **1985**, *24*, 629.
(428) Sheldrick, W. S.; Kroner, J.; Zwaschka, F.; Schmidpeter, A. *Angew. Chem., Int. Ed.* **1979**, *91*, 998.
(429) Marenco, A. J.; Pedersen, D. B.; Wang, S. L.; Petryk, M. W. P.; Kraatz, H. B. *Analyst* **2009**, *134*, 2021.
(430) Kramer, D. N.; Gamson, R. M. *Anal. Chem.* **1958**, *30*, 251.
(431) Pavlov, V.; Xiao, Y.; Willner, I. *Nano Lett.* **2005**, *5*, 649.
(432) DeFrank, J. J.; White, W. E. *Handb. Environ. Chem.* **2002**, *3*, 295.
(433) Taranekar, P.; Huang, C. Y.; Advincula, R. C. *Polymer* **2006**, *47*, 6485.
(434) Costero, A. M.; Gil, S.; Parra, M.; Mancini, P. M. E.; Martinez-Manez, R.; Sancenon, F.; Royo, S. *Chem. Commun* **2008**, 6002.
(435) Costero, A. M.; Parra, M.; Gil, S.; Gotor, R.; Mancini, P. M. E.; Martinez-Manez, R.; Sancenon, F.; Royo, S. *Chem.—Asian J.* **2010**, *5*, 1573.
(436) Ramanathan, M.; Wang, L.; Wild, J. R.; Meyeroff, M. E.; Simonian, A. L. *Anal. Chim. Acta* **2010**, *667*, 119.
(437) Pohanka, M.; Karasova, J. Z.; Kuca, K.; Pikula, J.; Holas, O.; Korabecny, J.; Cabal, J. *Talanta* **2010**, *81*, 621.

(438) Prokofieva, D. S.; Voitenko, N. G.; Gustyleva, L. K.; Babakov, V. N.; Savelieva, E. I.; Jenkins, R. O.; Goncharov, N. V. *J. Environ. Monit.* **2010**, *12*, 1349.
(439) Climent, E.; Marti, A.; Royo, S.; Martinez-Manez, R.; Marcos, M. D.; Sancenon, F.; Soto, J.; Costero, A. M.; Gil, S.; Parra, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5945.
(440) Jenkins, A. L.; Uy, O. M.; Murray, G. M. *Anal. Chem.* **1999**, *71*, 373.
(441) Jenkins, A. L.; Uy, O. M.; Murray, G. M. *Anal. Commun.* **1997**, *34*, 221.
(442) Huh, J. O.; Do, Y.; Lee, M. H. *Organometallics* **2008**, *27*, 1022.
(443) Knapton, D.; Burnworth, M.; Rowan, S. J.; Weder, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 5825.
(444) Khan, M. A. K.; Long, Y. T.; Schatte, G.; Kraatz, H. B. *Anal. Chem.* **2007**, *79*, 2877.
(445) Obare, S. O.; De, C.; Guo, W.; Haywood, T. L.; Samuels, T. A.; Adams, C. P.; Masika, N. O.; Murray, D. H.; Anderson, G. A.; Campbell, K.; Fletcher, K. *Sensors* **2010**, *10*, 7018.
(446) Crooks, R. M.; Ricco, A. J. *Acc. Chem. Res.* **1998**, *31*, 219.
(447) Dale, T. J.; Rebek, J. *J. Am. Chem. Soc.* **2006**, *128*, 4500.
(448) Petsalakis, I. D.; Lathiotakis, N. N.; Theodorakopoulos, G. *THEOCHEM* **2008**, *867*, 64.
(449) Han, S. F.; Xue, Z. W.; Wang, Z.; Wen, T. B. *Chem. Commun.* **2010**, *46*, 8413.
(450) Zheng, X. Y.; Okolotowicz, K.; Wang, B. L.; MacDonald, M.; Cashman, J. R.; Zhang, J. *Chem-Biol. Interact.* **2010**, *187*, 330.
(451) Akthakul, A.; Maklakov, N.; White, J. *Anal. Chem.* **2010**, *82*, 6487.
(452) Kim, T. H.; Kim, D. G.; Lee, M.; Lee, T. S. *Tetrahedron* **2010**, *66*, 1667.
(453) March, J. C.; Rao, G.; Bentley, W. E. *Appl. Microbiol. Biotechnol.* **2003**, *62*, 303.
(454) Wu, C. F.; Cha, H. J.; Rao, G.; Valdes, J. J.; Bentley, W. E. *Appl. Microbiol. Biotechnol.* **2000**, *54*, 78.
(455) Wu, C. F.; Cha, H. J.; Valdes, J. J.; Bentley, W. E. *Biotechnol. Bioeng.* **2002**, *77*, 212.
(456) Schofield, D. A.; Westwater, C.; Barth, J. L.; DiNovo, A. A. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 1383.
(457) Josse, D.; Lockridge, O.; Xie, W. H.; Bartels, F.; Schopfer, L. M.; Masson, P. *J. Appl. Toxicol.* **2001**, *21*, S7.
(458) Allert, M.; Rizk, S. S.; Looger, L. L.; Hellinga, H. W. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 7907.
(459) Rizk, S. S.; Cuneo, M. J.; Hellinga, H. W. *Protein Sci.* **2006**, *15*, 1745.
(460) Simonian, A. L.; diSioudi, B. D.; Wild, J. R. *Anal. Chim. Acta* **1999**, *389*, 189.
(461) Mulchandani, A.; Pan, S. T.; Chen, W. *Biotechnol. Prog.* **1999**, *15*, 130.
(462) Simonian, A. L.; Grimsley, J. K.; Flounders, A. W.; Schoeniger, J. S.; Cheng, T. C.; DeFrank, J. J.; Wild, J. R. *Anal. Chim. Acta* **2001**, *442*, 15.
(463) Heleg-Shabtai, V.; Gratziany, N.; Liron, Z. *Electrophoresis* **2006**, *27*, 1996.
(464) Havrilla, G. J.; Miller, T. C. *Rev. Sci. Instrum.* **2005**, 76.
(465) Zheng, J. Y.; Constantine, C. A.; Zhao, L.; Rastogi, V. K.; Cheng, T. C.; DeFrank, J. J.; Leblanc, R. M. *Biomacromolecules* **2005**, *6*, 1555.
(466) Bruno, J. G.; Carrillo, M. P.; Phillips, T.; Vail, N. K.; Hanson, D. *J. Fluoresc.* **2008**, *18*, 867.
(467) Hartmann-Thompson, C.; Keeley, D. L.; Pollock, K. M.; Dvornic, P. R.; Keinath, S. E.; Dantus, M.; Gunaratne, T. C.; LeCaptain, D. J. *Chem. Mater.* **2008**, *20*, 2829.
(468) Malosse, L.; Buvat, P.; Ades, D.; Siove, A. *Analyst* **2008**, *133*, 588.
(469) Bencic-Nagale, S.; Sternfeld, T.; Walt, D. R. *J. Am. Chem. Soc.* **2006**, *128*, 5041.
(470) Iski, E.; Horne, S. N.; DiCesare, J. C. *Abstr. Pap, ACS Natl. Meet.* **2004**, *227*, No. CHED.
(471) Kelly, M. T.; Bocarsly, A. B. *Coord. Chem. Rev.* **1998**, *171*, 251.
(472) Mitchell, M. B.; Sheinker, V. N.; Mintz, E. A. *J. Phys. Chem. B* **1997**, *101*, 11192.
(473) Aurian-Blajeni, B.; Boucher, M. M. *Langmuir* **1991**, *5*, 170.
(474) Sohn, H.; Letant, S.; Sailor, M. J.; Trogler, W. C. *J. Am. Chem. Soc.* **2000**, *122*, 5399.
(475) Letant, S. E.; Sailor, M. J. *Adv. Mater.* **2000**, *12*, 355.
(476) Courtney, R. C.; Gustafson, R. L.; Westerback, S. J.; Hyytiainen, H.; Chaberek, S. C., Jr.; Martell, A. E. *J. Am. Chem. Soc.* **1957**, *79*, 3030.
(477) Blaskó, A.; Bunton, C. A.; Hong, Y. S.; Mhala, M. M.; Moffatt, J. R.; Wright, S. *J. Phys. Org. Chem.* **1991**, *4*, 618.
(478) Adekunle, A. S.; Pillay, J.; Ozoemena, K. I. *Electroanalysis* **2008**, *20*, 2587.
(479) Kim, Y.; Lee, S.; Choi, H. H.; Noh, J. S.; Lee, W. *Nanotechnology* **2010**, 21.
(480) Wang, Y. Y.; Yang, Z.; Hou, Z. Y.; Xu, D.; Wei, L. M.; Kong, E. S. W.; Zhang, Y. F. *Sens. Actuators, B* **2010**, *150*, 708.
(481) Ganji, M. D.; Tajbakhsh, M.; Laffafchy, M. *Solid State Sci.* **2010**, *12*, 1547.
(482) Khan, M. A. K.; Keirman, K.; Petryk, M.; Kraatz, H. B. *Anal. Chem.* **2008**, *80*, 2574.
(483) Diakowski, P. M.; Xiao, Y. Z.; Petryk, M. W. P.; Kraatz, H. B. *Anal. Chem.* **2010**, *82*, 3191.
(484) Kong, L. T.; Wang, J.; Fu, X. C.; Zhong, Y.; Meng, F. L.; Luo, T.; Liu, J. H. *Carbon* **2010**, *48*, 1262.
(485) Kong, L. T.; Wang, J.; Luo, T.; Meng, F. L.; Chen, X.; Li, M. Q.; Liu, J. H. *Analyst* **2010**, *135*, 368.
(486) Black, R. M.; Muir, B. *J. Chromatogr. A* **2003**, *1000*, 253.
(487) Xu, L.; Gong, X. Y.; Lee, H. K.; Hauser, P. C. *J. Chromatogr. A* **2008**, *1205*, 158.
(488) Kanaujia, P. K.; Tak, V.; Pardasani, D.; Gupta, A. K.; Dubey, D. K. *J. Chromatogr. A* **2008**, *1185*, 167.
(489) Wang, Q. Q.; Gu, M. S.; Feng, J. L.; Ruan, J. X. *Chin. J. Anal. Chem.* **2006**, *34*, 5.
(490) Wang, Q. Q.; Xie, J. W.; Gu, M. S.; Feng, J. L.; Ruan, J. X. *Chromatographia* **2005**, *62*, 167.
(491) Creasy, W. R.; Rodriguez, A. A.; Stuff, J. R.; Warren, R. W. *J. Chromatogr. A* **1995**, *709*, 333.
(492) Le Moullec, S.; Begos, A.; Pichon, V.; Bellier, B. *J. Chromatogr. A* **2006**, *1108*, 7.
(493) Liu, Q.; Zhou, Y. X.; Meng, Z. H.; Wang, Q. Q.; Hu, X. Y.; Liu, Y. T. *Chin. J. Anal. Chem.* **2001**, *29*, 387.
(494) Ciner, F. L.; McCord, C. E.; Plunkett, R. W.; Martin, M. F.; Croley, T. R. *J. Chromatogr. B* **2007**, *846*, 42.
(495) Jakubowski, E. M.; Heykamp, L. S.; Durst, H. D.; Thomson, S. A. *Anal. Lett.* **2001**, *34*, 727.
(496) Abu-Qare, W.; Abou-Donia, B. *Chromatographia* **2001**, *53*, 251.
(497) Bryant, C. K.; LaPuma, P. T.; Hook, G. L.; Houser, E. J. *Anal. Chem.* **2007**, *79*, 2334.
(498) D'Agostino, P. A.; Hancock, J. R.; Chenier, C. L.; Lepage, C. R. J. *J. Chromatogr. A* **2006**, *1110*, 86.
(499) Hook, G. L.; Kimm, G.; Koch, D.; Savage, P. B.; Ding, B. W.; Smith, P. A. *J. Chromatogr. A* **2003**, *992*, 1.
(500) Hook, G. L.; Kimm, G.; Betsinger, G.; Savage, P. B.; Swift, A.; Logan, T.; Smith, P. A. *J. Sep. Sci.* **2003**, *26*, 1091.
(501) Shen, G.; Lee, H. K. *Anal. Chem.* **2002**, *74*, 648.
(502) Dubey, D. K.; Pardasani, D.; Gupta, A. K.; Palit, M.; Kanaujia, P. K.; Tak, V. *J. Chromatogr. A* **2006**, *1107*, 29.
(503) Lee, H. S. N.; Sng, M. T.; Basheer, C.; Lee, H. K. *J. Chromatogr. A* **2008**, *1196*, 125.
(504) Lee, H. S. N.; Sng, M. T.; Basheer, C.; Lee, H. K. *J. Chromatogr. A* **2007**, *1148*, 8.
(505) Lee, H. S. N.; Basheer, C.; Lee, H. K. *J. Chromatogr. A* **2006**, *1124*, 91.
(506) Pardasani, D.; Kanaujia, P. K.; Gupta, A. K.; Tak, V.; Shrivastava, R. K.; Dubey, D. K. *J. Chromatogr. A* **2007**, *1141*, 151.
(507) Kutuinen, M.-L.; Hartonen, K.; Riekkola, M.-L. *J. Microcolumn Sep.* **1991**, *3*, 505.

(508) Tørnes, J. A.; Opstad, A. M.; Johnsen, B. A. *Int. J. Environ. Anal. Chem.* **1991**, *44*, 227.
(509) Tørnes, J. A.; Opstad, A. M.; Johnsen, B. A. *Int. J. Environ. Anal. Chem.* **1991**, *44*, 209.
(510) Stan'kov, I. N.; Kondrat'ev, V. B.; Tsekhmister, V. I.; Derevyagina, I. D.; Sadovnikov, S. V.; Morozova, O. T.; Selivanova, V. I.; Kuz'mina, N. E.; Karaseva, I. E. *J. Anal. Chem.* **2010**, *65*, 1132.
(511) Stan'kov, I. N.; Kondrat'ev, V. B.; Glukhan, E. N.; Tsekhmister, V. I.; Sadovnikov, S. V.; Suchkov, A. P.; Derevyagina, I. D. *J. Anal. Chem.* **2010**, *65*, 174.
(512) Waysbort, D.; Manisterski, E.; Leader, H.; Manisterski, B.; Ashani, Y. *Environ. Sci. Technol.* **2004**, *38*, 2217.
(513) Groenewold, G. S.; Appelhans, A. D.; Gresham, G. L.; Olson, J. E.; Jeffery, M.; Weibel, M. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 69.
(514) Seiman, A.; Makarotseva, N.; Vaher, M.; Kaljurand, M. *Chem. Ecol.* **2010**, *26*, 145.
(515) Klemm, M. Device for extracting electrically charged molecules, useful e.g. in environmental monitoring or clinical diagnosis, comprises electrodes, containers and a matrix permeable to analyte. DE Patent 10149875, October 10, 2001.
(516) Christesen, S. D.; Jones, J. P.; Lochner, J. M.; Hyre, A. M. *Appl. Spectrosc.* **2008**, *62*, 1078.
(517) Timperley, C. M.; Casey, K. E.; Notman, S.; Sellers, D. J.; Williams, N. E.; Williams, N. H.; Williams, G. R. *J. Fluorine Chem.* **2006**, *127*, 1554.
(518) Rauk, A.; Shishkov, I. F.; Vilkov, L. V.; Koehler, K. F.; Kostyanovsky, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 7180.
(519) Koskela, H. *J. Chromatogr. B* **2010**, *878*, 1365.
(520) He, W. Y.; Du, F. P.; Wu, Y.; Wang, Y. H.; Liu, X.; Liu, H. Y.; Zhao, X. D. *J. Fluorine Chem.* **2006**, *127*, 809.
(521) Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Rohrbaugh, D. K. *J. Am. Chem. Soc.* **1990**, *112*, 6621.
(522) Van Den Berg, G. R.; Beck, H. C.; Benschop, H. P. *Bull. Environ. Contam. Toxicol.* **1984**, *33*, 505.
(523) Kaplan, D.; Shmueli, L.; Nir, I.; Waysbort, D.; Columbus, I. *Clean: Soil, Air, Water* **2007**, *35*, 172.
(524) Verweij, A.; Dekker, W. H.; Beck, H. C.; Boter, H. L. *Anal. Chim. Acta* **1983**, *151*, 221.
(525) Koskela, H.; Rapinoja, M. L.; Kuitunen, M. L.; Vanninen, P. *Anal. Chem.* **2007**, *79*, 9098.
(526) Gab, J.; Melzer, M.; Kehe, K.; Wellert, S.; Hellweg, T.; Blum, M.-M. *Anal. Bioanal. Chem.* **2010**, *396*, 1213.
(527) Albaret, C.; Lillet, D.; Auge, P.; Fortier, P.-L. *Anal. Chem.* **1997**, *69*, 2694.
(528) Koskela, H.; Hakala, U.; Vanninen, P. *Anal. Chem.* **2010**, *82*, 5331.
(529) Mandel, F. S.; Cox, R. H.; Taylor, R. C. *J. Magn. Reson.* **1974**, *14*, 235.
(530) Delpuech, J. J.; Peguy, A.; Khaddar, M. R. *J. Magn. Reson.* **1972**, *6*, 325.
(531) Engel, R.; Gelbaum, L. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1233.
(532) Kolakowski, J. E.; DeFrank, J. J.; Harvey, S. P.; Szafraniec, L. L.; Beaudry, W. T.; Lai, K. H.; Wild, J. R. *Biocatal. Biotransform.* **1997**, *15*, 297.
(533) Peters, J. A.; Nieuwenhuizen, M. S. *J. Magn. Reson.* **1985**, *65*, 417.
(534) Henderson, T. J. *Anal. Chem.* **2002**, *74*, 191.
(535) Amitai, G.; Adani, R.; Sod-Moriah, G.; Rabinovitz, I.; Vincze, A.; Leader, H.; Chefetz, B.; Leibovitz-Persky, L.; Friesem, D.; Hadar, Y. *FEBS Lett.* **1998**, *438*, 195.
(536) Hartmann-Thompson, C.; Hu, J.; Kaganove, S. N.; Keinath, S. E.; Keeley, D. L.; Dvornic, P. R. *Chem. Mater.* **2004**, *16*, 5357.
(537) Hartmann-Thompson, C.; Keeley, D. L.; Dvornic, P. R.; Keinath, S. E.; McCrea, K. R. *J. Appl. Polym. Sci.* **2007**, *104*, 3171.
(538) Saraswat, B. S.; Mason, J. *Polyhedron* **1986**, *5*, 1449.
(539) Ochocki, J.; Zurowska, B.; Mrozinski, J.; Kooijman, H.; Spek, A. L.; Reedijk, J. *Eur. J. Inorg. Chem.* **1998**, 169.
(540) Ng, S. W.; Das, V. G. K. *Acta Crystallogr.* **1996**, *C52*, 1373.
(541) Karthikeyan, S.; Ryan, R. R.; Paine, R. T. *Inorg. Chem.* **1989**, *28*, 2783.
(542) Millard, C. B.; Kryger, G.; Ordentlich, A.; Greenblatt, H. M.; Harel, M.; Raves, M. L.; Segall, Y.; Barak, D.; Shafferman, A.; Silman, I.; Sussman, J. L. *Biochemistry* **1999**, *38*, 7032.
(543) Guilbault, G. G.; Cannon, P. L.; Kramer, D. N. *Anal. Chem.* **1962**, *34*, 1437.
(544) Sohr, H.; Lohs, K. *J. Electroanal. Chem.* **1967**, *14*, 227.
(545) Mulchandani, P.; Mulchandani, A.; Kaneva, I.; Chen, W. *Biosens. Bioelectron.* **1999**, *14*, 77.
(546) Mulchandani, A.; Mulchandani, P.; Chen, W.; Wang, J.; Chen, L. *Anal. Chem.* **1999**, *71*, 2246.
(547) Mulchandani, A.; Mulchandani, P.; Kaneva, I.; Chen, W. *Anal. Chem.* **1998**, *70*, 4140.
(548) Campos, I.; Gil, L.; Martinez-Manez, R.; Soto, J.; Vivancos, J. L. *Electroanalysis* **2010**, *22*, 1643.
(549) Bohrer, F. I.; Sharoni, A.; Colesniuc, C.; Park, J.; Schuller, I. K.; Kummel, A. C.; Trogler, W. C. *J. Am. Chem. Soc.* **2007**, *129*, 5640.
(550) Pillay, J.; Ozoemena, K. I. *Electrochim. Acta* **2007**, *52*, 3630.
(551) Miller, K. A.; Yang, R. D.; Hale, M. J.; Park, J.; Fruhberger, B.; Colesniuc, C. N.; Schuller, I. K.; Kummel, A. C.; Trogler, W. C. *J. Phys. Chem. B* **2006**, *110*, 361.
(552) Joshi, K. A.; Prouza, M.; Kum, M.; Wang, J.; Tang, J.; Haddon, R.; Chen, W.; Mulchandani, A. *Anal. Chem.* **2006**, *78*, 331.
(553) Joshi, K. A.; Tang, J.; Haddon, R.; Wang, J.; Chen, W.; Mulchandani, A. *Electroanalysis* **2005**, *17*, 54.
(554) Pohanka, M.; Hrabinova, M.; Kuca, K. *Sensors* **2008**, *8*, 5229.
(555) Arduini, F.; Amine, A.; Moscone, D.; Ricci, F.; Palleschi, G. *Anal. Bioanal. Chem.* **2007**, *388*, 1049.
(556) Tiwari, D. C.; Sharma, R.; Vyas, K. D.; Boopathi, M.; Singh, V. V.; Pandey, P. *Sens. Actuators, B* **2010**, *151*, 256.
(557) Lee, C. Y.; Baik, S.; Zhang, J.; Masel, R. I.; Strano, M. S. *J. Phys. Chem. B* **2006**, *110*, 11055.
(558) Xie, Y. W.; Popov, B. N. *Anal. Chem.* **2000**, *72*, 2075.
(559) Choi, N. J.; Kwak, J. H.; Lee, D. D.; Huh, J. S.; Kim, J. C.; Park, K. B.; Park, J. S.; Shin, K. S.; Park, H. D. *J. Korean Phys. Soc.* **2004**, *45*, 1205.
(560) Wang, J.; Zima, J.; Lawrence, N. S.; Chatrathi, M. P.; Mulchandani, A.; Collins, G. E. *Anal. Chem.* **2004**, *76*, 4721.
(561) Wang, J.; Pumera, M.; Collins, G. E.; Mulchandani, A. *Anal. Chem.* **2002**, *74*, 6121.
(562) Wang, J.; Pumera, M.; Chatrathi, M. P.; Escarpa, A.; Musameh, M.; Collins, G.; Mulchandani, A.; Lin, Y.; Olsen, K. *Anal. Chem.* **2002**, *74*, 1187.
(563) Wang, J.; Chen, G.; Muck, A. *Anal. Chem.* **2003**, *75*, 4475.
(564) Hammond, M. H.; Johnson, K. J.; Rose-Pehrsson, S. L.; Ziegler, J.; Walker, H.; Caudy, K.; Gary, D.; Tillett, D. *Sens. Actuators, B* **2006**, *B116*, 135.
(565) Hu, S. Q.; Xie, J. W.; Xu, Q. H.; Rong, K. T.; Shen, G. L.; Yu, R. Q. *Talanta* **2003**, *61*, 769.
(566) Taranekar, P.; Baba, A.; Park, J. Y.; Fulghum, T. M.; Advincula, R. *Adv. Funct. Mater.* **2006**, *16*, 2000.
(567) Shulga, O. V.; Palmer, C. *Anal. Bioanal. Chem.* **2006**, *385*, 1116.
(568) Zuo, Y. J.; Yu, J. H.; Huang, Q. B.; Lin, Y. *Chin. J. Anal. Chem.* **2003**, *31*, 769.
(569) Corfield, G. C.; Ebdon, L.; Ellis, A. T. *Polym. Sci. Technol.* **1983**, *21*, 341.
(570) Corsi, R.; Culivicchi, G.; Sabatelli, F. *Trans — Geotherm. Resour. Counc.* **1985**, *9* (Part 2), 239.
(571) Pancrazio, J. J.; Keefer, E. W.; Ma, W.; Stenger, D. A.; Gross, G. W. *Neurotoxicology* **2001**, *22*, 393.
(572) Mulchandani, P.; Chen, W.; Mulchandani, A.; Wang, J.; Chen, L. *Biosens. Bioelectron.* **2001**, *16*, 433.
(573) Chen, J. C.; Shih, J. L.; Liu, C. H.; Kuo, M. Y.; Zen, J. M. *Anal. Chem.* **2006**, *78*, 3752.
(574) Seto, Y. *Yakugaku Zasshi* **2006**, *126*, 1279.
(575) Creasy, W. R.; Albro, T. G.; Cheicante, R.; Stuff, J. R. *Spectroscopy* **1994**, *9*, 42.

(576) Palliyaguru, L.; Sloss, J.; Rabitz, H.; Levis, R. J. *J. Mod. Opt.* **2008**, *55*, 177.
(577) Evans, R. A.; Jakubowski, E. M.; Muse, W. T.; Matson, K.; Hulet, S. W.; Mioduszewski, R. J.; Thomson, S. A.; Totura, A. L.; Renner, J. A.; Crouse, C. L. *J. Anal. Toxicol.* **2008**, *32*, 78.
(578) Grigoryan, H.; Schopfer, L. M.; Thompson, C. M.; Terry, A. V.; Masson, P.; Lockridge, O. *Chem-Biol. Interact* **2008**, *175*, 180.
(579) Williams, N. H.; Harrison, J. M.; Read, R. W.; Black, R. M. *Arch. Toxicol.* **2007**, *81*, 627.
(580) Butler, J.; Conoley, M. *LCGC North Am.* **2004**, 74.
(581) Mawhinney, D. B.; Hamelin, E. I.; Fraser, R.; Silva, S. S.; Pavlopoulos, A. J.; Kobelski, R. J. *J. Chromatogr. B* **2007**, *852*, 235.
(582) Richardson, D. D.; Caruso, J. A. *Anal. Bioanal. Chem.* **2007**, *389*, 679.
(583) Li, B.; Schopfer, L. M.; Hinrichs, S. H.; Masson, P.; Lockridge, O. *Anal. Biochem.* **2007**, *361*, 263.
(584) Shu, Y. R.; Su, A. K.; Liu, J. T.; Lin, C. H. *Anal. Chem.* **2006**, *78*, 4697.
(585) Ewing, K. J.; Lerner, B. *Appl. Spectrosc.* **2001**, *55*, 407.
(586) Ferrario, J. B.; Deleon, I. R.; Peuler, E. A. *Environ. Sci. Technol.* **1994**, *28*, 1893.
(587) Katagi, M.; Tatsuno, M.; Nishikawa, M.; Tsuchihashi, H. *J. Chromatogr. A* **1999**, *833*, 169.
(588) Kataoka, M.; Tsuge, K.; Takesako, H.; Hamazaki, T.; Seto, Y. *Environ. Sci. Technol.* **2001**, *35*, 1823.
(589) Matsuda, Y.; Nagao, M.; Takatori, T.; Niijima, H.; Nakajima, M.; Iwase, H.; Kobayashi, M.; Iwadate, K. *Toxicol. Appl. Pharmacol.* **1998**, *150*, 310.
(590) Noort, D.; Hulst, A. G.; Platenburg, D.; Polhuijs, M.; Benschop, H. P. *Arch. Toxicol.* **1998**, *72*, 671.
(591) Yeung, D. T.; Smith, J. R.; Sweeney, R. E.; Lenz, D. E.; Cerasoli, D. M. *J. Anal. Toxicol.* **2008**, *32*, 86.
(592) Kaipainen, A.; Kostiainen, O.; Riekkola, M. L. *J. Microcolumn Sep.* **1992**, *4*, 245.
(593) Goransson-Nyberg, A.; Fredriksson, S. A.; Karlsson, B.; Lundstrom, M.; Cassel, G. *Arch. Toxicol.* **1998**, *72*, 459.
(594) Renner, J. A.; Dabisch, P. A.; Evans, R. A.; McGuire, J. M.; Totura, A. L.; Jakubowski, E. M.; Thomson, S. A. *J. Anal. Toxicol.* **2008**, *32*, 92.
(595) Xu, L.; Lee, H. K. *Anal. Chem.* **2007**, *79*, 5241.
(596) Ekstrom, F. J.; Astot, C.; Pang, Y. P. *Clin. Pharmacol. Ther.* **2007**, *82*, 282.
(597) Gupta, A. K.; Palit, M.; Dubey, D. K.; Raza, S. K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1631.
(598) Noradoun, C. E.; Mekmaysy, C. S.; Hutcheson, R. M.; Cheng, I. F. *Green Chem.* **2005**, *7*, 426.
(599) Pardasani, D.; Gupta, A. K.; Palit, M.; Shakya, P.; Kanaujia, P. K.; Sekhar, K.; Dubey, D. K. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 3015.
(600) Piao, H.; Marx, R. B.; Schneider, S.; Irvine, D. A.; Staton, J. *J. Chromatogr. A* **2005**, *1089*, 65.
(601) Richardson, D. D.; Caruso, J. A. *Anal. Bioanal. Chem.* **2007**, *388*, 809.
(602) Wetherell, J. R.; Armstrong, S. J.; Read, R. W.; Clough, G. F. *Toxicol. Mech. Methods* **2008**, *18*, 313.
(603) Groenewold, G. S.; Appelhans, A. D.; Gresham, G. L.; Olson, J. E.; Jeffery, M.; Wright, J. B. *Anal. Chem.* **1999**, *71*, 2318.
(604) Rohrbaugh, D. K. *J. Chromatogr. A* **1998**, *809*, 131.
(605) Tsuchihashi, H.; Katagi, M.; Tatsuno, M.; Nishikawa, M.; Miki, A. In *Natural and Selected Synthetic Toxins*; American Chemical Society: Washington, DC, 2000; Vol. 745, p369.
(606) Wils, E. R. J.; Hulst, A. G. *J. Chromatogr.* **1990**, *523*, 151.
(607) Wils, E. R. J.; Hulst, A. G. *Fresenius J. Anal. Chem.* **1992**, *342*, 749.
(608) Boulet, C. A.; Dagostino, P. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *104*, 93.
(609) Smith, J. R.; Shih, M. L.; Price, E. O.; Platoff, G. E.; Schlager, J. J. *J. Appl. Toxicol.* **2001**, *21*, S35.
(610) Sass, S.; Fisher, T. L. *Org. Mass Spectrom.* **1979**, *14*, 257.
(611) Asbury, G. R.; Wu, C.; Siems, W. F.; Hill, H. H. *Anal. Chim. Acta* **2000**, *404*, 273.
(612) Steiner, W. E.; Clowers, B. H.; Matz, L. M.; Siems, W. F.; Hill, H. H. *Anal. Chem.* **2002**, *74*, 4343.
(613) Steiner, W. E.; Clowers, B. H.; Haigh, P. E.; Hill, H. H. *Anal. Chem.* **2003**, *75*, 6068.
(614) Takats, Z.; Wiseman, J. M.; Gologan, B.; Cooks, R. G. *Science* **2004**, *306*, 471.
(615) Palit, M.; Pardasani, D.; Gupta, A. K.; Shakya, P.; Dubey, D. K. *Anal. Bioanal. Chem.* **2005**, *381*, 477.
(616) Pardasani, D.; Mazumder, A.; Gupta, A. K.; Kanaujia, P. K.; Tak, V.; Dubey, D. K. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 3109.
(617) Martin, A. N.; Farquar, G. R.; Frank, M.; Gard, E. E.; Fergenson, D. P. *Anal. Chem.* **2007**, *79*, 6368.
(618) Tak, V.; Kanaujia, P. K.; Pardasani, D.; Kumar, R.; Srivastava, R. K.; Gupta, A. K.; Dubey, D. K. *J. Chromatogr. A* **2007**, *1161*, 198.
(619) Steiner, W. E.; Harden, C. S.; Hong, F.; Klopsch, S. J.; Hill, H. H.; McHugh, V. M. *J. Am. Soc. Mass Spectrom.* **2006**, *17*, 241.
(620) Yamaguchi, S.; Asada, R.; Kishi, S.; Sekioka, R.; Kitagawa, N.; Tokita, K.; Yamamoto, S.; Seto, Y. *Forensic Toxicol.* **2010**, *28*, 84.
(621) Smith, P. A.; Lepage, C. J.; Lukacs, M.; Martin, N.; Shufutinsky, A.; Savage, P. B. *Int. J. Mass Spectrom.* **2010**, *295*, 113.
(622) Zhang, Y. F.; Kubachka, K. M.; Caruso, J. A. *Anal. Methods* **2010**, *2*, 1243.
(623) D'Agostino, P. A.; Chenier, C. L. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 1617.
(624) McDaniel, L. N.; Romero, N. A.; Boyd, J.; Coimbatore, G.; Cobb, G. P. *Talanta* **2010**, *81*, 1568.
(625) Schopfer, L. M.; Grigoryan, H.; Li, B.; Nachon, F.; Masson, P.; Lockridge, O. *J. Chromatogr. B* **2010**, *878*, 1297.
(626) Gab, J.; John, H.; Melzer, M.; Blum, M. M. *J. Chromatogr. B* **2010**, *878*, 1382.
(627) Midey, A. J.; Miller, T. M.; Viggiano, A. A.; Bera, N. C.; Maeda, S.; Morokuma, K. *Anal. Chem.* **2010**, *82*, 3764.
(628) Kishi, S.; Sekioka, R.; Sodeyama, M.; Shiga, M.; Seto, Y. *Bunseki Kagaku* **2010**, *59*, 65.
(629) Kataoka, M.; Tsunoda, N.; Ohta, H.; Tsuge, K.; Takesako, H.; Seto, Y. *J. Chromatogr. A* **1998**, *824*, 211.
(630) Hu, X. Y.; Lou, Y. H.; Zhou, Y. X. *Chin. J. Anal. Chem.* **2001**, *29*, 957.
(631) Kataoka, M.; Tsuge, K.; Seto, Y. *J. Chromatogr. A* **2000**, *891*, 295.
(632) Pardasani, D.; Purohit, A.; Mazumder, A.; Dubey, D. K. *Anal. Methods* **2010**, *2*, 661.
(633) Subramaniam, R.; Astot, C.; Juhlin, L.; Nilsson, C.; Ostin, A. *Anal. Chem.* **2010**, *82*, 7452.
(634) Adams, T. K.; Capacio, B. R.; Smith, J. R.; Whalley, C. E.; Korte, W. D. *Drug Chem. Toxicol.* **2004**, *27*, 77.
(635) Li, B.; Ricordel, I.; Schopfer, L. M.; Baud, F.; Megarbane, B.; Nachon, F.; Masson, P.; Lockridge, O. *Toxicol. Sci.* **2010**, *116*, 23.
(636) John, H.; Breyer, F.; Thumfart, J. O.; Hochstetter, H.; Thiermann, H. *Anal. Bioanal. Chem.* **2010**, *398*, 2677.
(637) Debouit, C.; Bazire, A.; Lallement, G.; Daveloose, D. *J. Chromatogr. B* **2010**, *878*, 3059.
(638) Stubbs, S. J.; Read, R. W. *J. Chromatogr. B* **2010**, *878*, 1253.
(639) Tenberken, O.; Worek, F.; Thiermann, H.; Reiter, G. *J. Chromatogr. B* **2010**, *878*, 1290.
(640) van der Meer, J. A.; Trap, H. C.; Noort, D.; van der Schans, M. J. *J. Chromatogr. B* **2010**, *878*, 1320.
(641) Driskell, W. J.; Shih, M.; Needham, L. L.; Barr, D. B. *J. Anal. Toxicol.* **2002**, *26*, 6.
(642) Kumar, A. *JOM* **2000**, 52.
(643) Nieuwenhuizen, M. S.; Venema, A. *Mass-Sensitive Devices*; VCH: Weinheim, Germany, 1991.
(644) Harris, C. M. *Anal. Chem.* **2003**, *75*, 355A.
(645) Grate, J. W.; Rose-Pehrsson, S. L.; Venezky, D. L.; Klusty, M.; Wohltjen, H. *Anal. Chem.* **1993**, *65*, 1868.
(646) Grate, J. W. *Chem. Rev.* **2000**, *100*, 2627.

(647) Guilbault, G. G.; Tomita, Y.; Kolesar, E. S. *Sens. Actuators* **1981**, *2*, 43.
(648) Scheide, E. P.; Guilbault, G. G. *Anal. Chem.* **1972**, *44*, 1764.
(649) Shackelford, W. M.; Guilbault, G. G. *Anal. Chim. Acta* **1974**, *73*, 383.
(650) Guilbault, G. G.; Affolter, J.; Tomita, Y.; Kolesar, E. S., Jr. *Anal. Chem.* **1981**, *53*, 2057.
(651) Kristoff, J.; Guilbault, G. G. *Anal. Chim. Acta* **1983**, *149*, 337.
(652) Guilbault, G. G.Ngeh-Ngwainbi, J. *Biotec 2. Biosensors and environmental biotechnology*, Stuttgart, New York: Gustav Fischer-Verlag, 1988, Vol. 2, 17−22.
(653) Tomita, Y.; Guilbault, G. G. *Anal. Chem.* **1980**, *52*, 1484.
(654) Grate, J. W.; Kaganove, S. N. Strongly hydrogen-bond acidic polymer and methods of making and using. U.S. Patent 6,015,869, March 17, 1998.
(655) Lipskier, J. F.; Demathieu, C.; Chastaing, E. Polymeric materials absorbing organophosphorus compounds, their synthesis, and chemical sensors containing these materials. FR Patent 2784114, September 18, 1998.
(656) Hartmann-Thompson, C.; Keeley, D. L.; Voit, B.; Eichhorn, K. J.; Mikhaylova, Y. *J. Appl. Polym. Sci.* **2008**, *107*, 1401.
(657) Chen, D.; Xu, Y.; Li, D.; Xu, S.; Wang, X. *Electron. Lett.* **2010**, *46*, 1436.
(658) Jenkins, A. L.; Murray, G. M. *Anal. Chem.* **1996**, *68*, 2974.
(659) Nieuwenhuizen, M. S.; Harteveld, J. L. N. *Sens. Actuators, B* **1994**, *19*, 502.
(660) Nieuwenhuizen, M. S.; Harteveld, J. L. N. *Sens. Actuators, A* **1994**, *44*, 219.
(661) Guilbault, G. G.; Scheide, E. P. *J. Inorg. Nucl. Chem.* **1970**, *32*, 2959.
(662) Guilbault, G. G.; Kristoff, J.; Owens, D. *Anal. Chem.* **1985**, *57*, 1754.
(663) Kepley, L. J.; Crooks, R. M.; Ricco, A. J. *Anal. Chem.* **1992**, *64*, 3191.
(664) Chen, D.; Xu, Y.; Wang, J. J.; Zhang, L. Y. *Sens. Actuators, B* **2010**, *150*, 483.
(665) Nieuwenhuizen, M. S. SAW sensor for chemical warfare agents 3. Evaluation of some lanthanide co-ordination compounds as chemical interfaces using the nerve agent sarin. TNO Prins Maurits Laboratory, 1992.
(666) Nieuwenhuizen, M. S.; Harteveld, J. L. N. *Talanta* **1994**, *41*, 461.
(667) Nieuwenhuizen, M. S.; Harteveld, J. L. N. *Sens. Actuators, B* **1997**, *40*, 167.
(668) Dejous, C.; Rebiere, D.; Pistre, J.; Tiret, C.; Planade, R. *Sens. Actuators, B* **1995**, *B24*, 58.
(669) Crooks, R. M.; Yang, H. C.; McEllistrem, L. J.; Thomas, R. C.; Ricco, A. J. *Faraday Discuss* **1997**, *107*, 285.
(670) Thomas, R. C.; Yang, H. C.; DiRubio, C. R.; Ricco, A. J.; Crooks, R. M. *Langmuir* **1996**, *12*, 2239.
(671) Dominguez, D. D.; Chung, R.; Nguyen, V.; Tevault, D.; McGill, R. A. *Sens. Actuators, B* **1998**, *53*, 186.
(672) Pei, Z. F.; Ma, X. F.; Ding, P. F.; Zhang, W. M.; Luo, Z. Y.; Li, G. A. *Sensors* **2010**, *10*, 8275.
(673) Zhao, Y. Q.; Du, X.; Wang, X. Y.; He, J. H.; Yu, Y. B.; He, H. *Sens. Actuators, B* **2010**, *151*, 205.
(674) Shaffer, R. E.; Rose-Pehrsson, S. L.; McGill, R. A. *Field Anal. Chem. Technol.* **1998**, *2*, 179.
(675) Zellers, E. T.; Morishita, M.; Cai, Q. Y. *Sens. Actuators, B* **2000**, *B67*, 244.
(676) Cazaubon, C.; Levi, H.; Bordieu, C.; Rebiere, D.; Pistre, J. *Rev. Electr. Electron.* **1999**, 55.
(677) Cernosek, R. W.; Yelton, W. G.; Colburn, C. W.; Anderson, L. F.; Staton, A. W.; Osbourn, G. C.; Bartholomew, J. W.; Martinez, R. F.; Ricco, A. J.; Crooks, R. M. *Proc. SPIE Int. Soc. Opt. Eng.* **1999**, *3857*, 146.
(678) Williams, D.; Pappas, G. *Field Anal. Chem. Technol.* **1999**, *3*, 45.
(679) Hartmann-Thompson, C.; Keeley, D. L.; Gallagher, S. *Sens. Actuators, B* **2006**, *115*, 697.
(680) Gurton, K. P.; Felton, M.; Dahmani, R.; Ligon, D. *Appl. Opt.* **2007**, *46*, 6323.
(681) Huang, J.; Jiang, Y. D.; Du, X. S.; Bi, J. *Sens. Actuators, B* **2010**, *146*, 388.
(682) Voiculescu, I.; Zaghloul, M. E.; McGill, R. A.; Houser, E. J.; Fedder, G. K. *IEEE Sens. J.* **2005**, *5*, 641.
(683) Voiculescu, I. R.; Zaghloul, M. E.; McGill, R. A.; Vignola, J. F. *Proc. Inst. Mech. Eng., Part C* **2006**, *220*, 1601.
(684) Leis, J.; Zhao, W. C.; Pinnaduwage, L. A.; Gehl, A. C.; Allman, S. L.; Shepp, A.; Mahmud, K. K. *Digital Signal Process* **2010**, *20*, 1229.
(685) Zuo, G. M.; Li, X. X.; Li, P.; Yang, T. T.; Wang, Y. L.; Cheng, Z. X.; Feng, S. L. *Anal. Chim. Acta* **2006**, *580*, 123.
(686) ACS meeting, Washington D.C., 2009.