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Nucleophilic Polymers and Gels in Hydrolytic Degradation of Chemical Warfare Agents

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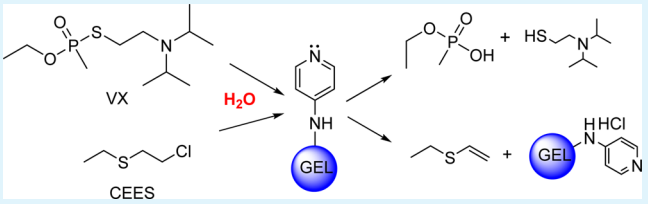
Supporting Information

ABSTRACT: Water- and solvent-soluble polymeric materials based on polyalkylamines modified with nucleophilic groups are introduced as catalysts of chemical warfare agent (CWA) hydrolysis. A comparative study conducted at constant pH and based on the criteria of the synthetic route simplicity, aqueous solubility, and rate of hydrolysis of CWA mimic, diisopropyl-fluorophosphate (DFP), indicated that 4-aminopyridine-substituted polyallylamine (PAAm-APy) and polyvinylamine substituted with 4-aminopyridine (PVAm-APy) were advantageous over 4-pyridinealdoxime-modified PVAm and PAAm, poly(butadiene-*co*-pyrrolidinopyridine), and PAAm modified with bipyridine and its complex with Cu(II). The synthesis of PVAm-APy and PAAm-APy involved generation of a betaine derivative of acrylamide and its covalent attachment onto the polyalkylamine chain followed by basic hydrolysis. Hydrogel particles of PAAm-APy and PVAm-APy cross-linked by epichlorohydrin exhibited pH-dependent swelling and ionization patterns that affected the rate constants of DFP nucleophilic hydrolysis. Deprotonation of the aminopyridine and amine groups increased the rates of the nucleophilic hydrolysis. The second-order rate of nucleophilic hydrolysis was 5.5- to 10-fold higher with the nucleophile-modified gels compared to those obtained by cross-linking of unmodified PAAm, throughout the pH range. Testing of VX and soman (GD) was conducted in 2.5−3.7 wt % PVAm-APy suspensions or gels swollen in water or DMSO/water mixtures. The half-lives of GD in aqueous PVAm-APy were 12 and 770 min at pH 8.5 and 5, respectively. Addition of VX into 3.5−3.7 wt % suspensions of PVAm-APy in DMSO-d_6 and D_2O at initial VX concentration of 0.2 vol % resulted in 100% VX degradation in less than 20 min. The unmodified PVAm and PAAm were 2 orders of magnitude less active than PVAm-APy and PAAm-APy, with VX half-lives in the range of 24 h. Furthermore, the PVAm-APy and PAAm-APy gels facilitated the dehydrochlorination reaction of sulfur mustard (HD) and its analogue 2-chloroethyl ethylsulfide (CEES). The ability of the reported aminopyridine-modified polyalkylamine materials to degrade the most persistent of CWAs, coupled with aqueous solubility, and the presence of numerous amino groups that provide convenient "handles" for covalent attachment on polymeric and inorganic supports yields promise for applications such as protective fabric and textile treatment and components of decontaminating materials.



KEYWORDS: *polyvinylamine, polyallylamine, nucleophilic polymers, chemical warfare agents, VX, HD, hydrogels, self-decontaminating fabrics*

INTRODUCTION

Self-detoxifying materials (SDM) capable of degradation of organophosphorous (OP) and blistering chemical warfare agents (CWA) and pesticides on contact are being developed for applications such as protective fabrics, garments, soft shelters, air filtration and heating, ventilation, and air conditioning systems. Hydrolytic and nucleophilic polymers represented by poly(vinyl alcohol−*co*-vinylamine), poly(ethylenimine), and polyacrylamidoxime have been reported to be suitable components for incorporation into SDM fibers and fabrics with enhanced moisture and gas transport characteristics.[1−5] Utilization of nucleophilic polymers and polymer colloids as well as polymer-modified nanoparticles affords efficient catalytic media, protective barriers and SDM capable of degrading and detoxifying CWA agents and pesticides.[4,6−13]

Nanomaterials such as nanotubular titania, anatase, and nanocrystalline TiO_2 enable exceptionally rapid degradation of VX in the presence of surface-adsorbed water; hence, these titania materials are considered to be promising candidates to

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impart reactivity with CWAs within chemically resistant paints for military vehicles.[14,15] However, it is a significant challenge to retain the reactivity of catalytic nanoparticles enabled by the nanomaterial's unique surface chemistry and porosity when they are imbedded within robust paints or coatings. In developing hydrogel materials discussed in this paper, we targeted soft, reactive matter that can be permanently linked to fabric without significant loss of reactivity; the hydrogel can imbibe sufficient quantities of water to enable self-decontaminating capability. When impregnated into a porous matrix and cross-linked, the polymer layer can be locked stably into the matrix.

We have previously reported a facile degradation of CWA by α-nucleophilic polyacrylamidoxime (PANOx) and poly(*N*-hydroxyacrylamide) (PHA) in their amidoximate and oximate forms, respectively, in the presence of water.[12] While nontoxic and exceptionally active in CWA hydrolysis, these α-nucleophilic polymers are thermally and chemically unstable; PANOx is harder to engineer into protective coatings or fabrics due to its insolubility in water or common organic solvents caused by the inherently present glutaroimide−dioxime cross-links. In the present work, we set out to design polymers stable at ambient and moderately elevated temperatures, capable of hydrolyzing CWA, soluble in water or organic solvents, and readily cross-linkable and processable into components of functional porous matrices, including fabrics. Textile modification with responsive hydrogels can result in high value added, functional materials.[15−19]

Incorporation of responsive hydrogel alters interyarn pores or fiber−fiber distances in the fabrics, leading to changes in the textile permeability in response to the changes in the hydrogel swelling. We were interested in the possibility of altering the hydrogel's reactivity, concomitant with the changes in swelling caused by the changes in pH. We therefore applied a design where polymer nucleophilicity is enhanced by postsynthetic modification of a pH-responsive polyalkylamine main chain with groups that further augment the overall nucleophilicity of the polymer. Unmodified polyalkylamines are quite nucleophilic, as each of their units contains an active lone pair of electrons on the very electronegative nitrogen atom. These electrons are attracted to the positive parts of other molecules. In this work, we modified polyalkylamines with alkylaminopyridine, bipyridine, 4-pyridinealdoxime, and 4-pyrrolidinopyridine groups. Polyamines modified with aminopyridines appeared to be readily cross-linkable, yielding pH-responsive gels with hydrolytic capabilities that were dramatically pH-dependent.

In a comparative study where several series of related polymers modified by various nucleophilic groups were tested for the rate of DFP hydrolysis at a fixed pH, the hydrolysis in the presence of polyalkylamines modified with 4-aminopyridine groups was as rapid as the one in the presence of more potent nucleophiles such as polymers containing 4-pyridinealdoxime and pyrrolidinopyridine side chains. Furthermore, it was found that 4-aminopyridine-modified polyalkylamines enabled rapid degradation of nerve agents VX and soman, with the hydrolysis half-lives on the order of 10−30 min.

Beyond nerve agents, the nucleophile-modified polyalkylamines also caused facile hydrolysis of the blistering agents, sulfur mustard and its analogue CEES, in the presence of water, thus demonstrating certain versatility of the polymers of the present study as self-detoxifying materials.

EXPERIMENTAL SECTION

Materials. Polyallylamine (PAAm) was prepared by neutralization of poly(allylamine hydrochloride) (M_w by GPC, 900 kDa, Sigma-Aldrich), by 2 M NaOH followed by the polymer dialysis against deionized water (membrane MWCO, 12−14 kDa) and lyophilization. Poly(butadiene-*co*-maleic anhydride) (polyBMA, nominal molecular weight, 10−15 kDa, butadiene/anhydride mol ratio, 1:1) was obtained as a 25% solution in acetone from Polysciences, Inc. (Warrington, PA) and was concentrated and dried under vacuum prior to use. Pyridine-4-carboxaldoxime was purchased from VWR (97%). 2-Chloroethyl ethyl sulfide (98%, CEES) and diisopropylfluorophosphate (99%) DFP) were obtained from Sigma-Aldrich Chemical Co. CWA isopropyl methylphosphonofluoridate (sarin or GB), pinacolyl methylphosphonofluoridate (soman or GD), and *S*,2-diisopropylaminoethyl methylphosphonothioate (VX) were obtained from the Chemical Agent Standard Analytical Reference Material program at the U.S. Army Edgewood Chemical Biological Center. The agent purities were determined by liquid NMR and confirmed by gas chromatography with thermal conductivity detection. Purities of GD, GB, and VX were 97, 97, and 95 wt %, respectively. All handling of the CWA was conducted in a chemical surety laboratory certified for supertoxic compounds.

Caution. Median lethal inhalation concentration (LCt50) to 50% of exposed population for GD and VX is 50 and 10 mg min^{-1} m^{-3}, respectively. *Ct* refers to the concentration of the vapor or aerosol in the air multiplied by the time the individual is exposed. These compounds are extremely hazardous and should only be handled by trained personnel following appropriate safety precautions. All other chemicals, buffers, and solvents were obtained from Sigma-Aldrich Chemical Co. and were of the highest purity available.

Syntheses. *4-Aminopyridine-Substituted Polyallylamine (PAAm-APy) and Polyvinylpyridine (PVAm-APy).* Syntheses of PAAm and PVAm modified with 4-aminopyridine (PAAm-APy) involved generation of cyanopyridine derivative of acrylamide, 1-(3-amino-3-oxopropyl)-4-cyanopyridin-1-ium chloride, CAS 105624-84-8 (AmCyPy, Figure S1). In brief, a solution of 5.2 g (50 mmol) 4-cyanopyridine and 3.6 g (50 mmol) acrylamide in 100 mL isopropanol was mixed with 15 mL of concentrated hydrochloric acid in 50 mL of isopropanol, which was added gently under stirring. The reaction mixture was brought to 50 °C; the resulting slurry was stirred and kept at 90 °C under reflux for 1.5 h. Then the mixture was allowed to equilibrate at ambient temperature overnight, the resulting white solids were separated by suction filtering and extensively washed with chilled isopropanol and dried under vacuum at 50 °C until constant weight. Calcd %: C, 51.1; H, 4.76; N, 19.9. Found %: C, 51.5; H, 4.83; N, 20.16. Melting point: 187 °C. ^{1}H NMR (400 MHz, D_2O): δ 3.0 (t, 2H, CH_2 α to amide), 5.3 (t, 2H, CH_2 α to N^+), 8.8 (d, 2H, pyridinium CH), 9.4 (d, 2H, pyridinium CH). For the PAAm modification (Figure S2), an aqueous solution containing 5.3 g (25 mmol) of AmCyPy and 2.8 g polyallylamine (50 mmol) (100 mL total) was allowed to react under stirring at 40 °C for 4 h. Then 30 mL of 50% aqueous NaOH were added into the solution, which was stirred at 90 °C for another 4 h. The mixture was allowed to equilibrate at ambient temperature, the polymer was precipitated by acetone, redissolved in deionized water, and the solution was dialyzed against excess aqueous sodium methoxide (pH 8.5, membrane MWCO, 12−14 kDa) and lyophilized. ^{1}H NMR (400 MHz, D_2O): δ 2.61 (m, CH_2 α to −N), 2.86, 3.11 (m, CH_2 α to −N-CR), 5.95, 6.1 (m, secondary −NH), 6.5 (m, pyridine), 7.9, 8.5 (m, 2H pyridine). With the use of integrations of signals at 2.61 (methylene of allylamine) to 8.5 ppm (pyridine), it was estimated that the degree of polyallylamine's amine group modification was approximately 50 mol %. That is, 50% of the polymer $-NH_2$ groups were substituted with 4-aminopyridine moiety.

Synthesis of Polyvinylamine and PVAm-APy. PVAm (weight-average MW, 62 kDa) was synthesized by free-radical polymerization of N-vinylformamide (NVF) followed by basic hydrolysis and purification of the PNVF as described in detail previously.[11] For the modified PVAm synthesis (PVAm-APy), a procedure identical to the

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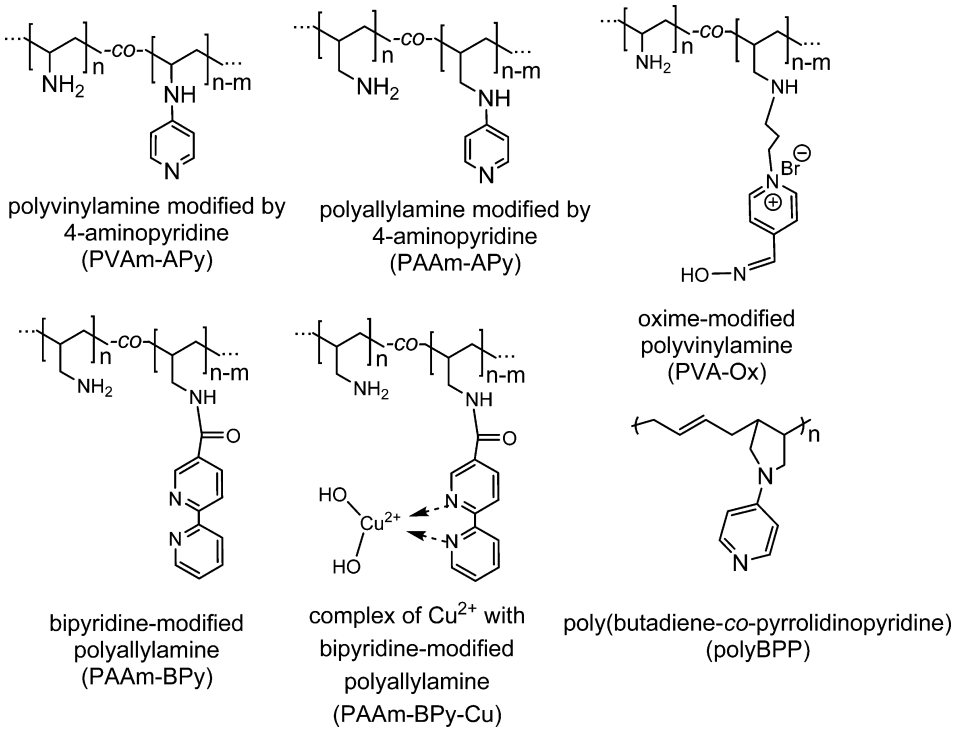

Figure 1. Structures of polymers of the present study.

Table 1. Properties of Polymers Studied

polymer species	nominal molecular weight (g/mol)	average molecular weight of monomeric unit (g/mol)	aqueous solubility	degree of modification (mol % relative to amino groups)[b]
polyvinylamine (PVAm)	62000	43	+	0
polyallylamine (PAAm)	900000	58	+	0
PVAm-APy	62000	82	+	50%
PAAm-APy	900000	87	+	50%
PAAm-BPy	900000	148	+	50%
PAAm-BPy-Cu	900000	197	−	50%[a]
PVAm-Ox	62000	80	+	10%
PVAm-Ox	62000	103	+	20%
polyBPP	10000−15000	214	−	50%[c]

[a]Elemental analysis shows ca. 1:1 (mol/mol) Cu^{2+}/bipyridine group. [b]From ^{1}H NMR integrations. [c]Ratio of pyrrolidinopyridine groups per total content of monomeric units.

one with PAAm was utilized. With the use of integrations of ^{1}H NMR signals at 3.7 (methylenes of polyvinylamine) to 8.5 ppm (pyridine), it was estimated that the degree of PVAm modification was approximately 50 mol %, similar to PAAm-APy. ^{1}H NMR (400 MHz, D_2O): δ 1.53 (m, CH, β to − NH), 2.10 (m, CH_2 α to −NH), 2.7, 2.9 (m, CH_2 α to −N-CR), 3.8 (m, −NH), 5.95, 6.1 (m, secondary −NH), 6.7 (m, pyridine), 8.5 (m, 2H pyridine). For the CWA hydrolysis studies, the PVAm-APy and PAAm-APy polymers were dialyzed against deionized water (MWCO, 12−14 kDa), with pH adjusted to 9.2 using minute quantities of 1 M NaOH. After dialysis, the samples were snap-frozen in liquid nitrogen and lyophilized.

Synthesis of PVAm-APy and PAAm-APy Gels Cross-Linked by Epichlorohydrin.[20] Solution of PAAm-APy (2.18 g, 25 mmol), PVAm-APy (2.05 g, 25 mmol), or PAAm (MW, 1.45 g, 25 mmol) in 75 mL water (pH adjusted to 10) was chilled to 4 °C in a refrigerator. Epichlorohydrin (0.2 mL, 2.5 mmol) was dissolved in the polymer solution and immediately mixed with a solution of sorbitane trioleate (0.5 mL) in 120 mL toluene under vigorous stirring. The mixture was kept at 60 °C for 4 h under magnetic stirring (1000 rpm) and the hydrocarbon phase was decanted. The solids were filtered and suspended in isopropanol (100 mL) under stirring. The formed cross-linked beads were filtered off, repeatedly rinsed by water and lyophilized to dryness. The gel particles were spherical and sized in the 50−200 μm range (Figure S3). Syntheses of 4-pyridinealdoxime-modified polyvinylamine (PVAm-Ox), polyallylamine modified with bipyridine (PAAm-BPy), and its complex with copper (PAAm-BPy-Cu), and supernucleophilic poly(butadiene-*co*-pyrrolidinopyridine) (polyBPP) were conducted following the procedures described previously.[6,21−27] Details of the synthesis and characterization of these polymers are given in S4 . Chemical structures of the synthesized polymers are shown in Figure 1 and polymer parameters are collected in Table 1.

METHODS

Evaluation of the DFP hydrolysis by ^{31}P NMR. The kinetics of DFP degradation hydrolyzed by polymers and gels was assessed by liquid state ^{31}P NMR spectrometry using a Bruker Avance III HD 400 spectrometer (161.98 MHz). The reaction milieu consisted of 50 mM of the following buffers: trisodium citrate (pH 4.0−5.5), MES (pH 5.5−6.7), AMPD (pH 7.8−9.7), and CAPS (pH 9.7−11.5). For medium preparation, the buffer compounds were dissolved in D_2O,

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and pH was adjusted by adding minute quantities of 1 M NaOH or HCl solutions. A polymer solution or suspension of a given concentration and pH was first prepared and vigorously stirred by a magnetic bar at 500 rpm, wherein a proper amount of DFP was added via a syringe, the mixture was sonicated for 5 s and at a specified time interval since the DFP addition, 0.7 mL of the liquid were withdrawn and immediately placed in an NMR tube and measurements commenced. The spectra were recorded at 25 °C by accumulation of 64 scans. The reaction time was taken to be the midpoint of the acquisition period. The reaction conversions degree (F) at different time intervals were calculated from the ratios of the signal integration of the hydrolysis product (diisopropylphosphate, DIPP) versus the sum of ^{31}P signal integrations of the product and the reactant (DFP) in ^{31}P NMR, eq 1,

$$F = \Sigma I_p/(\Sigma I_r + \Sigma I_p) \quad (1)$$

where ΣI_r and ΣI_p are the sums of the integrations of the signals corresponding to the reactant (DFP) and product (DIPP), respectively. The reaction was found to follow pseudo-first-order reaction kinetics, eq 2, and the observed reaction rate constant k_{obs} was obtained from the initial slope of linear plots $\ln(1 - F)$ versus t. The reaction half-life ($t_{1/2}$) and the second-order reaction rate (k'') were derived as in eqs 3 and 4, where C_0 and C_{cat} represent the initial DFP concentration and the catalyst concentration, respectively.

$$\ln(1 - F) = -k_{obs}t \quad (2)$$

$$t_{1/2} = \ln(2)/k_{obs} \quad (3)$$

$$k'' = k_{obs}/C_{cat} \quad (4)$$

Evaluation of VX and GD degradation in polymer solutions was conducted using high resolution ^{31}P NMR. A weighed sample (between 10 and 30 mg) was placed in a 5 mm glass liquid NMR tube. Solvent was used (a mixture of 400 μL DMSO-d_6 and 60 μL D_2O) to help swell the polymer into a gel (although the DMSO did not appear to produce as much swelling as water at pH 6) and to maintain a single liquid phase with the CWA. Neat CWA was added to the NMR tube and mixed to start the kinetic runs, using 1 μL of GD or 4 μL VX, depending on the experiment. Reaction of the CWA was monitored by a JEOL ECS-400 NMR, using a 5 mm broadband liquids gradient probe at ambient (20−22 °C) temperature. The following parameters were used: detection frequency, 161.83 MHz; offset, 10 ppm; sweep width, 400 ppm; number of scans, 32 or higher; relaxation delay, 3 s; excite angle, 30°; excite pulse length, 7.4 μs; total acquisition time, 4 min for early kinetic points <20 min after mixing, and up to 32 min for later points; autoreceiver gain, on; 65536 data points; proton decoupling with the WALTZ sequence, and no NOE irradiation. Some experiments with GD were conducted in 100% aqueous solution with PVAm-APy with 4 μL of GD and with the solution pH adjusted by adding glacial acetic acid to produce a pH 5 or 8 solution.

Study of the CEES Degradation by ^{1}H NMR. Degradation reactions of 2-chloroethyl ethylsulfide (CEES), a simulant of sulfur mustard, in the presence of nucleophilic polymers were studied in a heterogeneous, three-phase system. The nucleophilic PVAm-APy and PAAm-APy gels cross-linked by epichlorohydrin were allowed to swell in aqueous buffer and CEES dissolved in deuterated chloroform ($CDCl_3$). Experimental procedures involved were similar to those developed for heterogeneous reactions we reported previously.[12] In brief, a weighed amount (10−100 mg) of gel particles were equilibrated with aqueous 2-amino-2-methylpropane-1,3-diol (AMPD) buffer (0.2 M, pH 9.1) for 3 days. An aqueous suspension of the swollen gels (1 mL) was blended with 2 mL of freshly prepared CEES solution with a known initial CEES concentration in $CDCl_3$. Biphenyl (0.2 M) in $CDCl_3$ was utilized as an internal reference enabling concentration measurement (Figure S5). The suspension was sonicated for a specified time t using an Aquasonic model 75T ultrasonic cleaner (power, ∼ 380 W, VWR Scientific) to enable a proper contact between CEES and gel particles in aqueous phase. Sonication was intermittent, to avoid heating the reaction mixture. At specified time t_2, the aqueous gel phase and $CDCl_3$ phase were separated with a 15 s centrifugation (15000 rpm) and 0.7 mL of the chloroform phase was subjected to ^{1}H NMR spectrometry using a Bruker Avance 400 spectrometer operating at 400 MHz. Determination of products was accomplished using NMR and ESI-MS spectroscopy.

Studies of Sulfur Mustard Degradation. These were conducted using high-resolution proton and ^{13}C NMR. A weighed sample of PVAm-APy of 12−17 mg was placed in a 5 mm glass liquids NMR tube. Solvent was used (a mixture of 400 μL DMSO-d6 and 60 μL D_2O) to help swell the polymer into a gel and to maintain a single liquid phase with HD. Neat, nonisotopically labeled HD [bis(2-chloroethyl)sulfide] was added (2 μL) to the NMR tube and mixed to start the kinetic runs. Reaction of the CWA was monitored by a JEOL ECS-400 NMR, using a 5 mm broadband liquids gradient probe at ambient (20−22 °C) temperature. Kinetics were measured using proton NMR. The following parameters were used: single pulse experiment; detection frequency, 399.78 MHz; offset, 5 ppm; sweep width, 15 ppm; number of scans, 16−32; relaxation delay, 4 s; excite angle, 90°; excite pulse length, 12 μs; total acquisition time, 20−30 min; autoreceiver gain, on; 65536 data points, and no decoupling or NOE irradiation.

^{13}C NMR was used to confirm the spectral assignments, using a detection frequency of 100.52 MHz; offset, 100 ppm; sweep width, 300 ppm; number of scans, 2048; relaxation delay, 10 s; excite angle, 60°; excite pulse length, 11 μs; total acquisition time, 390 min; auto receiver gain, on; 32768 data points; proton decoupling with WALTZ sequence; and no NOE irradiation. The divinyl sulfide product had peaks with a chemical shift of 115 and 130 ppm, referenced to the D_2O solvent lock.

Measurement of Gel Swelling. To measure the equilibrium water content (S) at room temperature, dry networks of known weights (W_d) were placed into excess aqueous buffer (10 mM) at a certain pH, where they were kept at 25 °C in sealed vials for 5−10 days. The swelling kinetics were monitored by weighing the gel samples and, upon reaching constant weights, swollen gels were gently wiped up and weighed to give W_s. The equilibrium swelling degree was expressed by S (%) = $100(W_s/W_d - 1)$, where W_s and W_d represent the weight of swollen and dry samples, respectively, and was obtained for each gel and pH combination in triplicate.

Microgel Titration and ζ-Potential Measurements. To obtain the apparent pK_a and ionization degree (α) of the gel particles, bulk titration was performed at 25 ± 1 °C using a 736 GP Titrino potentiometric titration system (Metrohm Ltd.). Titration of microgels in their acidic form was carried out in a degassed 10 mM NaCl solution with 0.01−0.1 M NaOH as a titrant, at 0.2−0.5 wt % polymer concentrations. The titration was carried out slowly for 8 h to allow for proper equilibration. The resulting titration curves yielded inflection points, which enabled calculation of the apparent pK_a of the titratable groups: $pK_a = pH + \log[(1 - \alpha)/\alpha]$, where α is the degree of dissociation (the ratio of the free amino/pyridine groups to the total monomeric units concentration; the free titratable group concentration was found from the volume of NaOH added at each pH.[28] The potential at the surface of shear (ζ-potential) of the 0.02 wt % gel suspensions in 10 mM NaCl, with pH adjusted to a desired value by adding 5 M NaOH or HCl, was measured using a NanoBrook ZetaPALS zeta potential analyzer (Brookhaven Instruments Co.) with built-in software employing the Smoluchowski ζ-potential model. At the chosen salt concentration, the Debye length [$\kappa^{-1} = 0.304/([NaCl])^{1/2}$] was of the order of 3 nm, while the swollen microgel particles were of 150−250 μm in radius (r). Therefore, we were well within the Helmholtz−Smoluchowski limit ($r\kappa \rightarrow \infty$), where the simple expression of Smoluchowski is valid, and the ζ-potential is roughly equal to the diffuse layer potential.[28]

RESULTS AND DISCUSSION

Hydrolytic Activity of Nucleophilic Polymers. The electron-deficient phosphorus center of the OP compounds represents a convenient target for hydrolytic attack by

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nucleophiles; multiple structure−reactivity studies show correlations for reaction rates of OPs with different classes of nucleophiles.[27,29−34] Hydrolytic reactivities are sensitive to the substrate structure, nucleophile type and basicity, nature of the leaving group, solvent type, and solvation factors.[35,36]

The rate of a bimolecular nucleophilic substitution reaction, the S_N2 mechanism, depends on the ease of the leaving group displacement as well as the nucleophilicity of the attacking group. The easier it is for the leaving group to come off the OP ester, the faster will be its hydrolysis. Diisopropylfluorophosphate (DFP), sarin (*O*-isopropyl methylphosphonofluoridate), and soman (*O*-pinacolyl methylphosphonofluoridate, GD) that possess very similar leaving groups will have similar hydrolytic reactivities, making DFP a close mimic of these and other V-type chemical warfare agents. Similarly, the greater the nucleophilicity of the attacking group, the faster will the product be formed. The relative availability of the electrons in attacking the positive centers of the OP substrate determines the nucleophile's relative propensity for hydrolytic reactions. It must be noted that a charged nucleophile is less potent than its protonated amine.[37] Because protonation decreases the nucleophilicy of a species, the pH of the medium affects the rate of hydrolytic reactions. The relationship between protonation and the pH depends on the pK_a of the nucleophile. Thus, at a fixed pH, the most reactive group is usually the one with the lowest pK_a. These reasons led us to base our comparative study on DFP as a simulant of organophosphate CWA and the reactions with various designed nucleophiles were conducted at the same, moderately basic pH of 8.7 that is slightly below the pK_a of the majority of the nucleophilic groups of the polymers under study (except the oximate and 2,2′-bipyridine groups) and where the rate constant of the spontaneous hydrolysis by hydroxyls (k_0) is elevated but still significantly smaller than the rate of the nucleophilic aminolysis by the catalytic groups (k''_N). The observed DFP hydrolysis rate constant that is measured in our experiments, $k_{obs} = k_0 + k''_N C_{cat}$, is the sum of the spontaneous and nucleophilic rate constants; C_{cat} is the total effective concentration of the catalytic groups in aqueous solutions or suspensions, which was set at 10 mM in the comparative study.

The results of the DFP hydrolysis kinetics tests in an aqueous buffer with concentrations determined by ^{31}P NMR at pH 8.7 are shown in Figure 2 and comparative results are collected in Table 2. As shown in Figure 2, the hydrolysis kinetics are described well by the pseudo-first order model, with excellent linear fits in the coordinates of eq 2 ($R^2 > 0.97$ in all cases). The reaction was also first order with respect to the initial nucleophilic polymer concentration (C_{cat}) (Figure S6). In all experiments, the only phosphorus-containing product of the DFP hydrolysis was diisopropylphosphate (Figure S7).

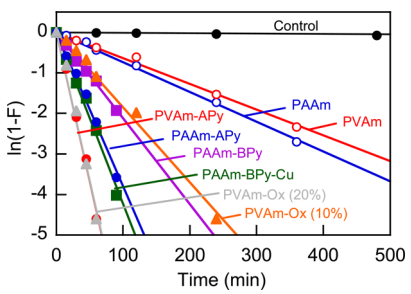

Figure 2. Representative kinetics of DFP hydrolysis catalyzed by polymer solutions in aqueous buffer. Initial conditions: DFP concentration, 5 mM; polymer concentration, 10 mM (per monomeric unit); buffer: AMPD, 50 mM in D_2O, pD 8.7.

Table 2. Half-Life ($t_{1/2}$) and Second-Order Rate Constant of Diisopropylfluorophosphate (DFP) Nucleophilic Hydrolysis (k''_N) in 50 mM Aqueous 2-Amino-2-methyl-1,3-propanediol (AMPD) Buffer at pH 8.7 and 25 °C

polymer species	$t_{1/2}$ (min)	$k''_N = (k_{obs} - k_{control})/C_{cat}$ (M^{-1} min^{-1})[a]
control (buffer only)	640	n/a
polyvinylamine (PVAm)	108	0.53
polyallylamine (PAAm)	96	0.61
PVAm-APy	10	7.2
PAAm-APy	18	3.7
PAAm-BPy	33	2.0
PAAm-BPy-Cu	16	4.1
PVAm-Ox[b]	37	1.7
PVAm-Ox[c]	10	7.2
polyBPP	12	5.5

[a]Initial polymer (C_{cat}) and DFP concentrations are 10 mM (on a monomer basis) and 5 mM, respectively. [b]Substitution, 10%. [c]Substitution, 20%.

Figure 2 and Table 2 show that modification of polyamines (PAAm, PVAm) with nucleophilic 4-aminopyridine (APy), bipyridine (BPy), and pyridine-4-carboxaldoxime (Ox) groups augmented the rates of the DFP hydrolysis in all cases, compared to the hydrolysis in the presence of unmodified PVAm and PAAm. Of all nucleophilic groups studied, pyrrolidinopyridine has frequently been described as the most efficient nucleophilic catalyst in acylation reactions of hindered alcohols,[38] hydrolysis of *p*-nitrophenylacetate[6] and analogous reactions. 4-Pyrrolidinopyridine (pK_a = 18.3) is a stronger *N*-heteroaromatic electron donor than pyridine (pK_a = 12.5),[39] 2,2′-bipyridine (pK_a 4.3),[40] or 4-aminopyridine (pK_a 9.2−9.4[41]). pK_a of pralidoxime is 7.8−8.1.[42−44]

It is somewhat counterintuitive to observe that the hydrolysis rates with PVAm-APy were equal to those with the significantly more powerful nucleophile, Ox, and were higher than with other polymers of the study, including polyBPP (Table 2). This result can be explained by factors other than the modifying group's nucleophilicity, such as the higher content of the APy than Ox in the polyvinylamine species, and also by the mass transfer limitations in the case of polyBPP and PAAm-BPy-Cu, which possess limited solubility in water and thus, were suspended rather than dissolved in the aqueous buffer. The accessibility of the nucleophilic catalytic groups by DFP in the polymer particles must be limited compared to that in the molecular solutions. Likewise, the faster hydrolysis with polyvinylamine-based solutions over polylallylamine-based ones can be related to the mass transfer limitations in the case of polyallylamine, solutions of which are considerably more viscous than PVAm solutions, given over an order of magnitude higher molecular weight of the tested parent PAAm (0.9 MDa) versus PVAm (60 kDa) and their respective nucleophile-modified species.

pH-Responsive Behavior of Nucleophilic Polyamine Gels. The above screening of the polymers for DFP degradation shows that polyamines modified with amino-pyridine are promising as self-detoxifying materials due to their superior activity, aqueous solubility, and ease of synthesis. The polyamines can be readily cross-linked resulting in gels, which

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enables a number of engineering routes toward incorporation of the nucleophilic polymers into porous matrices such as fabrics and membranes. The results of potentiometric titration (Figure 3) and ζ-potential measurements (Figure 4) demonstrate pH-dependent ionization patterns of the amine and aminopyridine groups in the PAAm-APy and PVAm-APy hydrogels. As expected, the ζ-potential and ionization degree increased with decreasing pH, indicating the presence of protonated amine and aminopyridine groups.

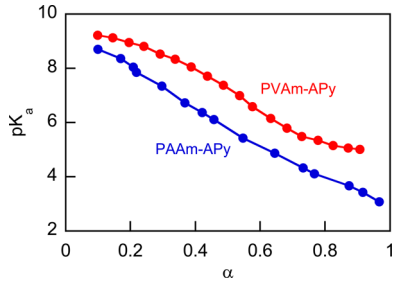

Figure 3. Potentiometric titration of PAAm-APy and PVAm-APy gels in aqueous 10 mM NaCl at 25 °C. pK_a and α are the apparent dissociation constant and degree of ionization, respectively.

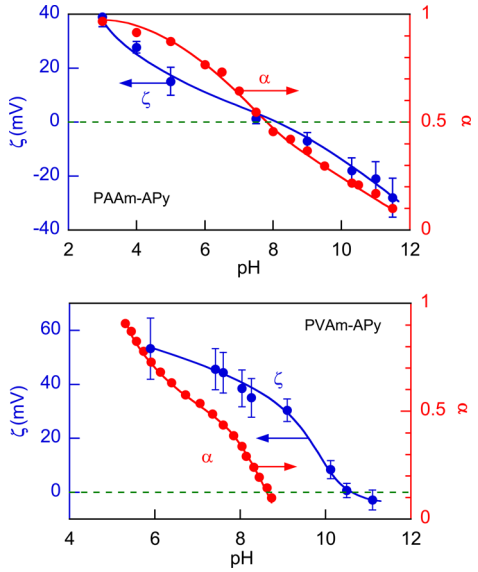

Figure 4. pH-Dependencies of ζ-potential (ζ) and degree of ionization (α) of cross-linked PAAm-APy and PVAm-APy gels in 10 mM NaCl at 25 °C.

It is interesting to observe that the PVAm-APy gels possessed significantly sharper pH-dependency of the degree of ionization than did their PAAm-APy counterparts, spanning the whole range of α within 3.2 pH units versus 8.5 units in the case of PAAm-APy. These differences, also observed previously with unmodified PVAm and PAAm, can be related to the differences in the probability of the protonation of an amine unit that is strongly influenced by the methylene spacer between amino groups and the polymer backbone, present in PAAm and absent in PVAm.[45]

The PVAm-APy gel particles became uncharged at $\alpha \approx 0.15$ (pH $\sim$ 10), whereas in the case of the PAAm-APy gels, the isoelectric point (ζ = 0 mV) was observed at $\alpha \approx 0.5$ (pH 8–9). In comparison, pK_a values of unmodified PVAm and PAAm hydrochlorides were reported to be ~10 and 9.7, respectively, with about 50% of the amino groups protonated at pH 7 and 8.7, respectively.[45−48] These values correspond very well to our results with modified polymers (Figure 4). Such a similarity between the pK_a values of the parent and modified PAAm and PVAm probably stems from the fact that the pK_a of 9.2 of the 4-aminopyridine group used for modification is quite close to the pK_a of the parent polyamines and thus approximately 50% modification of the primary amino groups in the polyamines with 4-aminopyridine group did not significantly alter the ionization behavior of the resulting polymers.

Figure 5 depicts the pH-dependent swelling of the aminopyridine-modified polyamine gels.

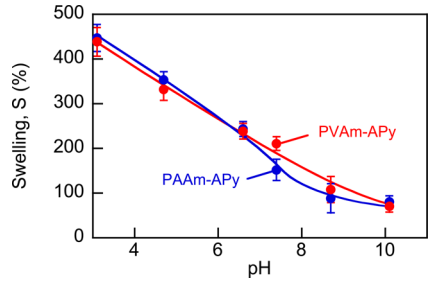

Figure 5. Effect of pH on equilibrium swelling degree (S) of cross-linked PAAm-APy and PVAm-APy gels in 10 mM NaCl at 25 °C.

Deprotonation of the charged groups led to a marked (5-fold) reduction of the gel swelling at basic pH. At the same time, the rates of nucleophilic hydrolysis increased. The second-order rate constant (k_N'') of the hydrolysis caused by the nucleophilic groups of the gel can be expressed as

$$k_N'' = (k_{obs} - k_0)/C_{cat}$$

where k_{obs} and k_0 are the rate constants for the observed pseudo-first order reaction in the presence of the catalyst (gel) and the spontaneous hydrolysis at the same pH without the gel, respectively, and C_{cat} is the effective concentration of catalytic groups.

Monotonic dependences of k_N'' on pH were observed in the pH 7 to 11 range (Figure 6), indicating a good correlation between the concentration of deprotonated amino and aminopyridine groups and the rate of nucleophilic hydrolysis. Accuracy of the k_N'' value determination was estimated in a separate series of measurements to be approximately ±15%. The k_N'' values were observed to be higher by 5.5- to 10-fold with the nucleophile-modified gels compared to those obtained by the cross-linking of unmodified PAAm, throughout the pH

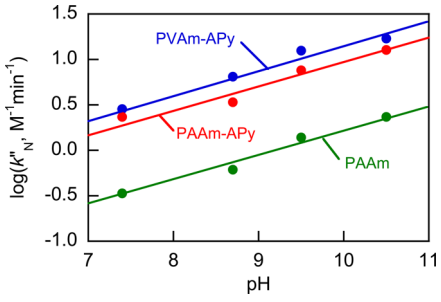

Figure 6. Effect of pH on the second-order rate constant of nucleophilic hydrolysis of DFP measured at 25 °C in 50 mM aqueous buffers at C_{cat} 10 mM and initial DFP concentration of 5 mM.

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range. The slopes of the linear fits in the Brønsted-type plots (Figure 6) were in the 0.25−0.28 range (R^2 > 0.96 in all cases), which is consistent with a concerted aminolysis reaction at the phosphorus center (i.e., for water attack catalyzed by amine and/or pyridine groups), with the formation of DFP-polymer coordinate intermediates.[27,48−50]

Hydrolysis of Soman and VX. While we could conduct a detailed study of the nerve agent simulant, DFP, under effective mass transfer control conditions (see Figure 2), the hydrolysis kinetics of CWA such as soman (GD) and VX needed to be studied in a closed system without stirring, except for the 15 rps spinning of the NMR tube, due to the limitations posed by safety concerns. The kinetics were studied in a mixture of polar deuterated solvents, DMSO-d_6 and D_2O (87/13 vol/vol %). The presence of DMSO was necessary to dissolve VX, which is less water-soluble at high pH. The kinetic measurements commenced upon addition of small quantities of CWA directly to the polymers. The progress of soman and VX degradation was followed by ^{31}P NMR. (S-8, S-9) The relative intensity of the two GD doublets rapidly decreased over time, while the single signal centered at 21.4 ppm belonging to pinacolyl methylphosphonic acid (PMPA) increased. It has been shown that the four stereoisomers of soman hydrolyze equally quickly.[51] PVAm-APy degraded 75% of GD after 2 min and greater than 90% in 24 h.

Because of the sufficient aqueous solubility of GD,[51,52] we were able to study the kinetics of its degradation in aqueous polymer solutions under both basic and acidic pH conditions. The PVAm-APy and PAAm-APy polymers that had been lyophilized against water at pH 9.2 were dissolved in D_2O with the pH adjusted by adding successive aliquots (5 μL) of glacial acetic acid to the polymer solution. ^{31}P NMR spectrum integrations of the products and unreacted GD yielded the conversion degree (F) (Figure 7).

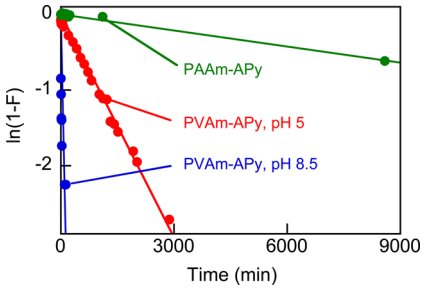

Figure 7. Representative kinetics of soman hydrolysis catalyzed by solutions of PVAm-APy in D_2O and PAAm−APy in DMSO-d_6/D_2O (87/13 vol/vol %). Initial loadings: PVAm-APy, 20 mg at pH 8.5 and 35 mg at pH 5; D_2O, 600 μL; PAAM-APy, 11 mg, GD, 4 μL; DMSO-d_6, 400 μL; D_2O, 60 μL.

The best-fit half-lives of GD in aqueous PVAm-APy solutions were 12 and 770 min at pH 8.5 and 5, respectively. Corresponding second-order hydrolysis rate constants ($k'' = k_{obs}/C_{cat}$) were 0.15 and 1.3 × 10^{-3} M^{-1} min^{-1} at pH 8.5 and 5, respectively. These results agree well with our observations of the nucleophilic hydrolysis of the CWA simulant, DFP ($t_{1/2}$ 10 min in Table 2), which demonstrated an analogous increase in k''_N upon pH change from 5 to 8.5 (see Figure 6). Soman is most stable in its aqueous solutions in the pH range of 4−6.[53] The hydrolysis of *O*-alkyl alkylphosphonofluoridates like DFP or soman was reported to proceed via the displacement mechanism through a formation of coordinated transition-state complexes with the attacking nucleophile and the leaving group being hydroxide and fluoride, respectively.[53] It can be hypothesized that the protonated primary amino groups and the nonprotonated 4-aminopyridine groups (minority at acidic pH) in PVAm-APy form multipodal transition state host−guest complexes with soman via hydrogen-bonding interactions that may both bind the target GD molecule and activate it toward hydrolysis.[54,55]

The decrease in the ^{31}P resonance intensity at 54 ppm and appearance of the resonance at 19 ppm showed hydrolysis of VX via formation of polymer-bound ethylmethylphosphonic acid (EMPA) by the cleavage of the electrophilic P−S bond (Figure S9). Addition of VX to a 3.5−3.7 wt % solution of PVAm-APy in DMSO-d_6 and D_2O (87/13 vol/vol %) at initial VX concentration of 0.2 vol % resulted in 100% VX degradation in less than 20 min (S-9). The unmodified parent PVAm and PAAm were 2 orders of magnitude less effective than their aminopyridine-modified derivatives, with VX half-lives within the range of 24 h. The catalytic cycle of VX hydrolysis in the presence of aminopyridine-modified polymer and water resulting in formation of EMPA and 2-(diisopropylamino)ethane-1-thiol as transient hydrolytic products is shown in Figure 8. The hypothetic mechanism depicted

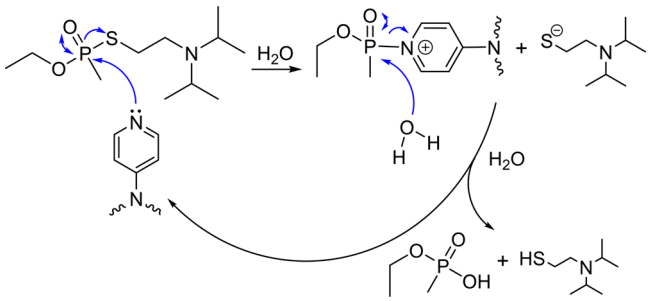

Figure 8. Schematic of the VX hydrolytic cycle catalyzed by an aminopyridine−modified polymer. The cycle involves complexation or VX with the nucleophilic groups of the polymer, enhancement of the electrophilic character of the P atom due to coordination, nucleophilic attack of water, and formation of the corresponding less toxic organophosphate derivative.

is analogous to the published intramolecular amino-group catalyzed hydrolysis and accounts for the formation of ionic species.[56,57] When the amount of water present and/or accessibility of the nucleophilic sites of the polymer are insufficient, the hydrolysis rate will diminish at appreciable degrees of CWA conversion due to the prevalence of the polymer-bound products, which decrease the effective concentration of the catalytic nucleophilic groups. The effect of water content above 10% on the VX hydrolysis in homogeneous solutions has been demonstrated previously.[56] VX reacts with an equimolar amount of water via exclusive P−S cleavage to produce the corresponding phosphonic acid (MeP(O)(OR)OH) and 2-aminoethanethiol ($HSCH_2CH_2NR_2$). In dilute aqueous solutions at neutral to weakly basic pH up to 9, VX hydrolyzes completely within 1 week with an initial observed pseudofirst-order rate constant of 1.9 × 10^{-4} min^{-1} at 23 °C,[56] which is 350 times slower than in our experiments in the presence of excess amino- and aminopyridine groups.

To the best of our knowledge, the only previously reported heterogeneous materials capable of hydrolyzing VX with half-lives in the 10−30 min range at ambient temperatures is

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nanotubular titania containing 20 wt % water[14] and α-nucleophilic polyacrylamidoximate (PANOx) containing up to 65% water.[12] Similar reactivity, aqueous solubility, and numerous amino groups present on aminopyridine-modified polyalkylamines that provide convenient "handles" for covalent attachment of these polymers on polymeric and inorganic supports certainly indicate that these polymers can be added to the arsenal of decontaminating materials.

Hydrolysis of CEES and Sulfur Mustard. Facile degradation of neurotoxic organophosphate CWA by the nucleophilic polymers described above prompts a question of whether the hydrolytic properties of our polymers would extend to degradation of blistering and tissue-injuring agents, bis(2-chloroethyl)sulfide (HD) and analogues (CEES), which are chemically unrelated to the OP esters, yet are quite reactive compounds. Reactivity of the sulfur mustards toward low-molecular weight amines in the presence of water is well-established.[58] Herein, we investigated the effect of 4-aminopyridine modified polyalkylamines on CEES in a heterogeneous water/organic solvent/solid system. The heterogeneous system included water-swollen, insoluble PVAm-APy or PAAm-APy gel particles that were brought in contact with a solution of CEES in chloroform. The $CDCl_3$ phase was analyzed by ^1H NMR and ESI-MS methods. In the absence of traces of water, CEES has been reported to be chemically stable in chloroform.[58] However, water-insoluble CEES undergoes hydrolysis on contact with water through a rapid formation of a transient cyclic sulfonium cation, which subsequently reacts with water, forming 2-ethylthioethanol, or with another CEES molecule, forming dimers at elevated initial CEES concentrations.[59,60] The sulfonium cation may also react with the amino groups of the gel, forming nucleophilic substitution products (Figure 9).

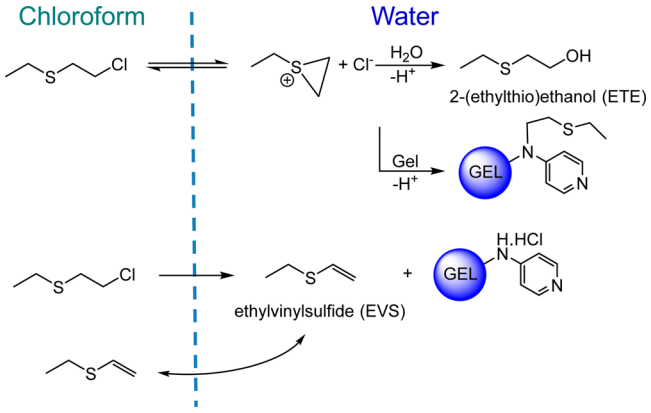

Figure 9. Schematic of the CEES hydrolysis and dehydrochlorination reactions in the triphasic water-swollen gel/water/chloroform system. The 4-aminopyridine moiety of the gel is shown to bind HCl in the dehydrochlorination and nucleophilic substitution reactions. The PVAm-APy and PAAm-APy gels possess multiple primary and secondary amino moieties capable of reacting with CEES. Reactions of the CEES dimerization are not shown; the dimers (m/z calculated, 195 or 213) were not found in the chloroform phase by ESI-MS.

The alkylation of the amine functionalities by CEES is known,[58,61] but detailed analysis of the products, if any, of the CEES reactions with our gels in the water phase was beyond the scope of the present study. No such products were found in the organic phase.

Notably, the formation of charged, water-soluble sulfonium cations will lead to the depletion of CEES in the chloroform phase, and thus, to the decrease of the relative intensity of the CEES proton resonances, measured by ^1H NMR in $CDCl_3$. A proper phase mixing by sonication led to a facile phase transfer of the reactants in our experiments, and therefore, the kinetics of the CEES disappearance was rapid (Figure 10). The CEES

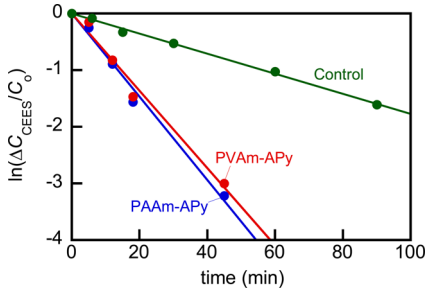

Figure 10. Kinetics of CEES disappearance from the organic phase on contact with water- swollen polyalkylamine modified with 4-aminopyridine gels PAAm-APy and PVAm-APy. Aqueous polymer concentration, 10 wt %. In the control experiment, the aqueous phase consisted of 0.2 M AMPD buffer (pH 9.2) without the gels. ΔC_{CEES} designates the change in the CEES concentration in $CDCl_3$ compared to the initial concentration C_0 set at 17.2 mM in all experiments.

disappearance in the organic phase followed the pseudo-first-order reaction mechanism, with the plots of $\ln(1 - F)$ versus time being linear ($R^2 > 0.98$ in all cases). The observed reaction half-times were measured to be 39, 10, and 9 min for the control (no gel, buffer only), PVAm-APy and PAAm-APy gels, respectively, being present in the aqueous phase. The role of the nucleophilic gels present in the aqueous phase is evident from the 4-fold enhancement of the CEES disappearance rate. The observed half-lives with the gels are 1.4-fold shorter than those previously reported for CEES (initial concentration, 17 mM) in 50 vol % aqueous acetone in the presence of a powerful nucleophile, sodium thiosulfate, at the 0.2 M level.[59]

Furthermore, the gels appeared to facilitate the dehydrochlorination reaction, which resulted in the appearance of ethylvinylsulfide (EVS) in the organic phase (Figure 9). EVS is soluble in both chloroform and water, so that only a fraction of the formed EVS could be detected in our measurements in $CDCl_3$. Nevertheless, at the initial PVAm-APy and PAAm-APy gel concentrations in the aqueous phase of 10 wt %, approximately 15 and 17 mol %, respectively, EVS concentration was measured in the organic phase relative to the initial CEES concentration, after a 1 h reaction. In the control experiment where 0.2 M AMPD buffer (pH 9.2) was used without the gels, EVS was barely found in the organic phase after 3 days (approximately 1−2 mol % relative to the initial CEES concentration). This result demonstrates the effect of the modified polyalkylamine gels on the hydrolytic CEES reactions. The gels significantly accelerated the CEES degradation.

The reactions of CWA sulfur mustard (HD) with solutions of un-cross-linked PVAm-APy and PAAm-APy were studied without sample stirring (except for spinning the NMR tube at 15 rps), to avoid exposure to the CWA. Polymer sample (12−17 mg) was dissolved or swelled in 400 μL DMSO-d_6 and 60 μL D_2O and subjected to ^1H NMR measurements as described in Experimental. Divinylsulfide (DVS) was the major reaction product that was detected soon (10−15 min) after the reaction commencement by its characteristic 1-ethylene ^1H signals in the 5.25 ppm area (Figure S5). HD sulfone (1-chloro-2-

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(ethylsulfinyl)ethane) or bis(2-choroethyl)sulfoxide was a minor product detectable after approximately 2 days of reaction, which probably resulted from the oxidation of HD by DMSO.[62] There was also an unidentified product in the proton spectrum, the small set of 8 peaks that are shifted from the divinylsulfide peaks. The degree of the HD conversion (F_{HD}) was calculated from the integrations ratio of the proton signals belonging to the products (both DVS and HD sulfone, area of 5.2 ppm) and methylene groups (α to C−S, area of 2.7 ppm)[63] of the residual HD, respectively. Figure 11 shows a

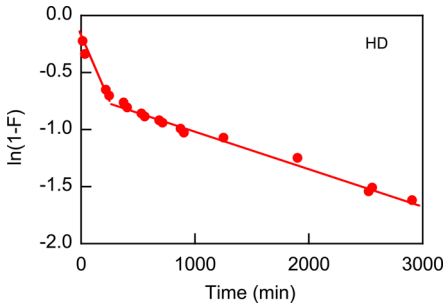

Figure 11. Kinetics of bis(2-chloroethyl)sulfide (HD) hydrolysis in the presence of PVAm-APy in a DMSO/water mixture. Initial conditions: polymer loading, 16.8 mg; DMSO-d_6, 400 μL; D_2O, 60 μL; T, 20 °C. The degree of HD conversion (F_{HD}) is calculated from the sums of the integrations of the ^{1}H signals corresponding to the reactant (HD) and product (see eq1).

typical HD hydrolysis kinetics in the presence of PVAm-APy polymer. The kinetics can be arbitrarily approximated by two straight lines yielding apparent k_{obs} of 0.3×10^{-3} and 1.9×10^{-3} min^{-1}, which correspond to half-lives of 36 and 6 h, respectively. These estimates of the half-life of HD in contact with the PVAm-APy polymer in DMSO that contained 13 vol % D_2O are ~2 orders of magnitude longer than in dilute HD solutions in D_2O (7 min[64]) but still by an order of magnitude shorter than in heterogeneous systems such as moist concrete.[65,66] Hydrolysis of HD in water is dependent on concentration and cosolvent, since HD is only slightly soluble in water at room temperature, so it typically forms insoluble droplets that are slow to react. To be practically effective, the polymer must not only react with HD but also aid in spreading out the HD over the surface. Further work is needed to determine the performance of the polymers to disperse HD over a range of pH values.

The biphasic shape of the kinetic curve is due to the initial rapid dehydrochlorination of HD, which produces HCl that binds to the primary amino and pyridine groups of the polymer, resulting in the salt formation. In the absence of stirring and sufficiently rapid dissociation of the salt, the number of the nucleophilic groups of the polymer available for catalysis of the hydrolysis is reduced, and thus, the kinetics becomes slower. This is a rather typical result where the catalytic sites are poisoned by the reaction product. In the case where sufficient amount of water is present and the mass transfer is rapid, the hydrolysis reactions do not change the rate until very high conversion degrees are achieved (compare with Figure 10).

In summary, our results with HD and CEES demonstrate that nucleophilic polyalkylamines are capable of facilitating the hydrolysis of these agents in a fashion similar to the previously reported low-molecular weight nucleophiles.[59] The rate of hydrolysis is strongly affected by the ability of the amino and aminopyridine groups to bind and dissociate from the hydrolysis products, thereby participating in the catalytic turnover.

CONCLUDING REMARKS

The ultimate goal in designing a reactive protective material is to destroy CWA, for example VX, the most toxic and persistent of the V-type CWAs, as rapidly and completely as possible.[14] The material could also provide protection against toxic industrial chemicals and other hazards. In that regard, it is of interest to compare the remarkable activity of the nucleophilic polyalkylamines described herein with reactive sorbents and decontaminants. Typically, complete destruction is desired within the time frame of 15 to 30 min, which has been achieved with liquid decontaminant, DS2, based on 70 wt % diethylenetriamine, 28 wt % ethylene glycol monomethyl ether, and 2 wt % sodium hydroxide.[52] The DS2 decontaminant is irritating to skin, potentially teratogenic, and unstable in the presence of moisture and air. Utilization of such a liquid as a component of gel-type materials intended for use in wearable garments or reactive sorbents can be ruled out. The more advanced and benign decontaminants, DF-200 and Decon Green and their variations capable of destroying a variety of chemical and biological agents within 10−30 min, include hydrogen peroxide or other peroxides and their activators as active components as well as a variety of surfactants, organic solvents, polymeric colloidal stabilizers, and other ingredients to afford a short-term colloidal stability as a foam or paste to the active decontaminant.[67,68] Decontaminants delivered as powdered solids typically need to be reconstituted with water prior to the use. In the present work, we introduced a novel route toward decontaminant development through utilization of nucleophilic and hydrophilic polymers that can be incorporated into porous matrices and fabrics and imbibe sufficient amounts of water enabling rapid and efficient hydrolysis of CWA. We demonstrated that aminopyridine-modified polyalkylamines are capable of rapidly hydrolyzing most persistent CWA, including VX and HD. In a parallel work, the same polymers modified with bromine were shown to kill anthrax spores. A certain versatility displayed by these polymers as decontaminants is encouraging. Our next steps will be to advance effective approaches for grafting of the polymers introduced in this work to engineered surfaces.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.5b06905.

Schematic of the synthesis of cyanopyridine derivative of acrylamide (AmCyPy), SEM image of PVAm-APy gel particles, detailed description of polymer syntheses and characterization, ^{1}H NMR spectra of freshly prepared solutions of CEES and ethylvinylsulfide, dependence of the observed rate constant of DFP hydrolysis on polymer concentration, ^{31}P NMR spectra of the hydrolysis of diisopropylfluorophosphate (DFP), ^{31}P NMR spectra of O-pinacolyl methylphosphonofluoridate, ^{31}P NMR spectra of *S*,2-diisopropylaminoethyl methylphosphonothioate (VX), and ^{1}H NMR spectrum of the HD reaction products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Gibson, P. W.; Schreuder-Gibson, H. L. Influence of Hydration State on Permeation Testing and Vapor Transport Properties of Protective Clothing Layers. *J. Engineered Fibers and Fabrics* **2009**, *4*, 11−20.

(2) Chen, L.; Bromberg, L.; Hatton, T. A.; Rutledge, G. C. Catalytic Hydrolysis of p-Nitrophenyl Acetate by Electrospun Polyacrylamidoxime Nanofibers. *Polymer* **2007**, *48*, 4675−4682.

(3) Chen, L.; Bromberg, L.; Schreuder-Gibson, H.; Walker, J.; Hatton, T. A.; Rutledge, G. C. Chemical Protection Fabrics via Surface Oximation of Electrospun Polyacrylonitrile Fiber Mats. *J. Mater. Chem.* **2009**, *19*, 2432−2438.

(4) Chen, L.; Bromberg, L.; Lee, J. A.; Zhang, H.; Schreuder-Gibson, H.; Gibson, P.; Walker, J.; Hammond, P. T.; Hatton, T. A.; Rutledge, G. C. Multifunctional Electrospun Fabrics via Layer-by-layer Electrostatic Assembly for Chemical and Biological Protection. *Chem. Mater.* **2010**, *22*, 1429−1436.

(5) Turaga, U.; Kendall, R. J.; Singhg, V.; Lalagiri, M.; Ramkumar, S. S. Advances in Materials for Chemical, Biological, Radiological and Nuclear (CBRN) Protective Clothing, Advances in Military Textiles and Personal Equipment; Sparks, E., Ed.; Woodhead: Oxford, U.K., 2012; pp 26−287.

(6) Narang, S. C.; Ventura, S.; Ramharack, R. Polymeric Dialkylaminopyridines as Supernucleophilic Catalysts, Chemical Reactions on Polymers. *ACS Symp. Ser.* **1988**, *364*, 72−80.

(7) Yang, Y. C.; Baker, J. A.; Ward, J. R. Decontamination of Chemical Warfare Agents. *Chem. Rev.* **1992**, *92*, 1729−1743.

(8) Bromberg, L.; Hatton, T. A. Nerve Agent Destruction by Recyclable Catalytic Magnetic Nanoparticles. *Ind. Eng. Chem. Res.* **2005**, *44*, 7991−7998.

(9) Bromberg, L.; Hatton, T. A. Decomposition of Toxic Environmental Contaminants by Recyclable Catalytic, Superparamagnetic Nanoparticles. *Ind. Eng. Chem. Res.* **2007**, *46*, 3296−3303.

(10) Bromberg, L.; Zhang, H.; Hatton, T. A. Functional Organic−Inorganic Colloids Modified by Iodoxybenzoic Acid. *Chem. Mater.* **2008**, *20*, 2001−2008.

(11) Bromberg, L.; Hatton, T. A. Poly(N-vinylguanidine): Characterization, and Catalytic and Bactericidal Properties. *Polymer* **2007**, *48*, 7490−7498.

(12) Bromberg, L.; Schreuder-Gibson, H.; Creasy, W. R.; McGarvey, D. J.; Fry, R. A.; Hatton, T. A. Degradation of Chemical Warfare Agents by Reactive Polymers. *Ind. Eng. Chem. Res.* **2009**, *48*, 1650−1659.

(13) Kim, K.; Tsay, O. G.; Atwood, D. A.; Churchill, D. G. Destruction and Detection of Chemical Warfare Agents. *Chem. Rev.* **2011**, *111*, 5345−5403.

(14) Wagner, G. W.; Chen, Q.; Wu, Y. Reactions of VX, GD, and HD with Nanotubular Titania. *J. Phys. Chem. C* **2008**, *112*, 11901−11906.

(15) Wagner, G. W.; Peterson, G. W.; Mahle, J. J. Effect of Adsorbed Water and Surface Hydroxyls on the Hydrolysis of VX, GD, and HD on Titania Materials: The Development of Self-Decontaminating Paints. *Ind. Eng. Chem. Res.* **2012**, *51*, 3598−3603.

(16) Jocic, D.; Tourrette, A.; Glampedaki, P.; Warmoeskerken, M. M. C. G. Application of Temperature and pH Responsive Microhydrogels for Functional Finishing of Cotton Fabric. *Mater. Technol.* **2009**, *24*, 14−23.

(17) Glampedaki, P.; Jocic, D.; Warmoeskerken, M. M.C.G. Moisture Absorption Capacity of Polyamide 6,6 Fabrics Surface Functionalised by Chitosan-Based Hydrogel Finishes. *Prog. Org. Coat.* **2011**, *72*, 562−571.

(18) Glampedaki, P.; Dutschk, V. Superabsorbent Finishes for Textiles, Functional Finishes for Textiles: Improving Comfort, Performance and Protection. Roshan, P., Ed.; Woodhead Publishing Series in Textiles; Elsevier: Cambridge, UK, 2014, 283−298.

(19) Bashari, A.; Hemmati Nejad, N.; Pourjavadi, A. Applications of Stimuli Responsive Hydrogels: a Textile Engineering Approach. *J. Text. Inst.* **2013**, *104*, 1145−1155.

(20) Gopalkrishna, K. M.; Thakaji, K. S.; Babu, B. S. Process for the Preparation of Crosslinked Polyallylamine Polymer, U.S. Patent 7,388,056, June 17, 2008.

(21) Shek, E.; Higuchi, T.; Bodor, N. Improved Delivery Through Biological Membranes. 2. Distribution, Excretion and Metabolism of N- Methyl-1, 6-dihydropyridine- 2- Carbaldoxime Hydrochloride, a Pro-drug of N- Methylpyridinium-2 carbaldoxime chloride. *J. Med. Chem.* **1976**, *19*, 108−112.

(22) Chennamaneni, S. R.; Vobalaboina, V.; Garlapati, A. Quaternary Salts of 4,30 and 4,40 bis-Pyridinium Monooximes: Synthesis and Biological Activity. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3076−3080.

(23) Bailey, M. M.; Heddleston, J. M.; Davis, J.; Staymates, J. L.; Hight Walker, A. R. Functionalized, Carbon Nanotube Material for the Catalytic Degradation of Organophosphate Nerve Agents. *Nano Res.* **2014**, *7*, 390−398.

(24) Blacker, N. C.; Findlay, P. H.; Sherrington, D. C. Synthesis of Cu-II-Complexed Polymers and Use as Catalysts in the Hydrolytic Decontamination of Sarin Nerve Agent. *Polym. Adv. Technol.* **2001**, *12*, 183−196.

(25) Narang, S.; Ventura, S. Immobilized 4-Dialkylaminopyridines: Supernucleophilic Chemical Decontaminating Agents, US Army Research Office Technical Report 23208.1-CH, 1987; http://handle.dtic.mil/100.2/ADA190999.

(26) Narang, S. C.; Ramharack, R. Poly(4-N-pyrrolidinopyridine) Copolymers as Supernucleophilic Reagents. *J. Polym. Sci., Polym. Lett. Ed.* **1985**, *23*, 147−150.

(27) Castro, E. A.; Echevarria, G. R.; Opazo, A.; Robert, P. S.; Santos, J. G. Kinetics and Mechanism of the Reactions of Polyallylamine with Aryl Acetates and Aryl Methyl Carbonates. *J. Phys. Org. Chem.* **2006**, *19*, 129−135.

(28) Bromberg, L.; Temchenko, M.; Hatton, T. A. Smart Microgel Studies. Polyelectrolyte and Drug-Absorbing Properties of Microgels from Polyether-Modified Poly(acrylic acid). *Langmuir* **2003**, *19*, 8675−8684.

(29) Harris, J. C. Rate of Hydrolysis In Handbook of Chemical Property Estimation Methods. *Environmental Behavior of Organic Compounds*; Lyman, W. J.; Reehl, W. F.; Rosenblatt, D. H., Eds. McGraw-Hill, New York, 1981; 7−48.

(30) Khan, S. A.; Kirby, A. J. The reactivity of Phosphate Esters. Multiple Structure−Reactivity Correlations for the Reactions of Triesters with Nucleophiles. *J. Chem. Soc. B* **1970**, 1172−1182.

(31) Wolfe, N. L. Organophosphate and Organophosphorothionate Esters: Application of Linear Free Energy Relationships to Estimate Hydrolysis Rate Constants for Use in Environmental Fate Assessment. *Chemosphere* **1980**, *9*, 571−579.

(32) Pregel, M. J.; Dunn, E. J.; Nagelkerke, R.; Thatcher, G. R. J.; Buncel, E. Alkali−Metal Ion Catalysis and Inhibition in Nucleophilic Displacement Reaction of Phosphorus−Sulfur−and Carbon−Based Esters. *Chem. Soc. Rev.* **1995**, *24*, 449−455.

(33) Jencks, W. P. A Primer for the Bema Hapothle. An Empirical Approach to the Characterization of Changing Transition-State Structures. *Chem. Rev.* **1985**, *85*, 511−527.

(34) Herschlag, D.; Jencks, W. P. Nucleophiles of High Reactivity in Phosphoryl Transfer Reactions: α-Effect Compounds and Fluoride Ion. *J. Am. Chem. Soc.* **1990**, *112*, 1951−1956.

(35) Bunnett, J. F. Nucleophilic Reactivity. *Annu. Rev. Phys. Chem.* **1963**, *14*, 271−290.

DOI: 10.1021/acsami.5b06905
ACS Appl. Mater. Interfaces 2015, 7, 22001−22011

(36) Edwards, J. O.; Pearson, R. G. The Factors Determining Nucleophilic Reactivities. *J. Am. Chem. Soc.* **1962**, *84*, 16−24.
(37) Larson, R. A.; Weber, E. J. *Reaction Mechanisms in Environmental Organic Chemistry*; CRC Press: Boca Raton, FL, 1994, 448.
(38) Höfle, G.; Steglich, W.; Vorbrüggen, H. Dialkylaminopyridines as Highly Active Acylation Catalysts. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.
(39) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. Extension of the Self-Consistent Spectrophotometric Basicity Scale in Acetonitrile to a Full Span of 28 pKa Units: Unification of Different Basicity Scales. *J. Org. Chem.* **2005**, *70*, 1019−1028.
(40) Öğretir, C.; Öztürk, İ. İ.; Tay, N. F. Quantum Chemical Studies on Acidity-Basicity Behaviors of Some Bipyridine Derivatives. *ARKIVOC* **2009**, No. xiv, 235−254.
(41) Smith, D. T.; Shi, R.; Borgens, R. B.; McBride, J. M.; Jackson, K.; Byrn, S. R. Development of Novel 4-Aminopyridine Derivatives as Potential Treatments for Neurological Injury and Disease. *Eur. J. Med. Chem.* **2005**, *40*, 908−917.
(42) Turarova, I.; Halamelc, K.; Koblina, Z. Study on Reactivation of Enzyme-Inhibitor Complexes by Oximes Using Acetylcholine Esterase Inhibited by Organophosphate Chemical Warfare Agents. *Enzyme Microb. Technol.* **1999**, *25* (3-5), 400−403.
(43) Rageh, N. M. Acidity Constants of Some Hydroxy Azo Pyrazolopyrimidines in Mixed Aqueous-Organic Solvents. *J. Chem. Eng. Data* **1998**, *43*, 373−377.
(44) Tiwari, S.; Ghosh, K. K.; et al. Spectrophotometric Determination of the Acidity Constants of Some Oxime-Based r-Nucleophiles. *J. Chem. Eng. Data* **2010**, *55*, 1153−1157.
(45) Sumaru, K.; Matsuoka, H.; Yamaoka, H. Exact Evaluation of Characteristic Protonation of Poly(vinylamine) in Aqueous Solution. *J. Phys. Chem.* **1996**, *100*, 9000−9005.
(46) Katchalsky, A.; Mazur, J.; Spitnik, P. General Behavior of Biocolloids and Polyelectrolytes in Solution. Polybase Properties of Polyvinylamine. *J. Polym. Sci.* **1957**, *23*, 513−532.
(47) Petrov, A. I.; Antipov, A. A.; Sukhorukov, G. B. Base−Acid Equilibria in Polyelectrolyte Systems: From Weak Polyelectrolytes to Interpolyelectrolyte Complexes and Multilayered Polyelectrolyte Shells. *Macromolecules* **2003**, *36*, 10079−10086.
(48) Shi, L.; Berkland, C. Acid-Labile Polyvinylamine Micro- and Nanogel Capsules. *Macromolecules* **2007**, *40*, 4635−4643.
(49) Kirby, A. J.; Jencks, W. P. The Reactivity of Nucleophilic Reagents toward the p-Nitrophenyl Phosphate Dianion. *J. Am. Chem. Soc.* **1965**, *87*, 3209−3216.
(50) Gresser, M. J.; Jencks, W. P. Ester Aminolysis. Structure-Reactivity Relationships and the Rate-Determining Step in the Aminolysis of Substituted Diphenyl Carbonates. *J. Am. Chem. Soc.* **1977**, *99*, 6963−6970.
(51) Ward, R. J.; Yang, Y.; Wilson, R. B.; Burrows, W. D.; Ackerman, L. L. Base-Catalyzed Hydrolysis of 1,2,2-Trimethylpropyl Methylphosphonofluoridate-An Examination of the Saturation Effect. *Bioorg. Chem.* **1988**, *16*, 12−16.
(52) Yang, Y.-C.; Baker, J. A.; Ward, J. R. Decontamination of Chemical Warfare Agents. *Chem. Rev.* **1992**, *92*, 1729−1743.
(53) Yli-Kauhaluoma, J.; Humppi, T.; Yliniemelä, A.; et al. Hydrolysis of Organophosphorus Nerve Agent Soman by the Monoclonal Antibodies Elicited against an Oxyphosphorane Hapten. *Acta Chem. Scand.* **1999**, *53*, 473−479.
(54) Hiscock, J. R.; Sambrook, M. R.; Cranwell, P. B.; Watts, P.; Vincent, J. C.; Xuereb, D. J.; Wells, N. J.; Raja, R.; Gale, P. A. Tripodal Molecules for the Promotion of Phosphoester Hydrolysis. *Chem. Commun.* **2014**, *50*, 6217−6220.
(55) Barba-Bon, A.; Costero, A. M.; Parra, M.; Gil, S.; Martnez-Manez, R.; Sancenon, F.; Gale, P. A.; Hiscock, J. R. Neutral 1,3-Diindolylureas for Nerve Agent Remediation. *Chem. - Eur. J.* **2013**, *19*, 1586−1590.
(56) Yang, Y.-C.; Szafraniec, L. L.; Beaudry, W. T.; Rohrbaugh, D. K.; Procell, L. R.; Samuel, J. B. Autocatalytic Hydrolysis of V-Type Nerve Agents. *J. Org. Chem.* **1996**, *61*, 8407−8413.
(57) Yang, Y.-C. Chemical Detoxification of Nerve Agent VX. *Acc. Chem. Res.* **1999**, *32*, 109−115.
(58) Wang, Q.-Q.; Begum, R. A.; Day, V. W.; Bowman-James, K. Sulfur, Oxygen, and Nitrogen Mustards: Stability and Reactivity. *Org. Biomol. Chem.* **2012**, *10*, 8786−8793.
(59) Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Ward, J. R. Kinetics and Mechanism of the Hydrolysis of 2-Chloroethyl Sulfides. *J. Org. Chem.* **1988**, *53*, 3293−3297.
(60) Yang, Y. C.; Szafraniec, L. L.; Beaudry, W. T.; Ward, J. R. Direct NMR Measurements of Sulfonium Chlorides Produced from the Hydrolyses of 2-Chloroethyl Sulfides. *J. Org. Chem.* **1987**, *52*, 1637−16338.
(61) Connors, T. A. Mechanism of Action of 2-Chloroethylamine Derivatives, Sulfur Mustards, Epoxides, and Aziridines, Antineoplastic and Immunosuppressive Agents. *Handbook of Experimental Pharmacology* **1975**, *38*, 18−34.
(62) Hsu, F. L.; Szafraniec, L. L.; Beaudry, W. T.; Yang, Y. C. Oxidation of 2-Chloroethyl Sulfides to Sulfoxides by Dimethyl sulfoxide. *J. Org. Chem.* **1990**, *55*, 4153−4155.
(63) Haapaniemi, E.; Mesilaakso, M. ^{1}H and ^{13}C{1H} NMR Spectral Parameters of Sulfur Mustards, Nitrogen Mustards, and Lewisites: Computing and Predicting of Reference Spectra for Chemical Identification. *Magn. Reson. Chem.* **2012**, *50*, 196−207.
(64) Logan, T. P.; Sartori, D. A. Nuclear Magnetic Resonance Analysis of the Solution and Solvolysis of Sulfur Mustard in Deuterium Oxide. *Toxicol. Mech. Methods* **2003**, *13*, 235−240.
(65) Brevett, C. A. S.; Sumpter, K. B.; Wagner, G. W.; Rice, J. S. Degradation of the Blister Agent Sulfur Mustard, Bis(2-chloroethyl) Sulfide on Concrete. *J. Hazard. Mater.* **2007**, *140*, 353−360.
(66) Brevett, C. A. S.; Sumpter, K. B.; Nickol, R. G. Kinetics of the Degradation of Sulfur Mustard on Ambient and Moist Concrete. *J. Hazard. Mater.* **2009**, *162*, 281−291.
(67) Love, A. H.; Bailey, C. G.; Hanna, M. L.; Hok, S.; Vu, A. K.; Reutter, D. J.; Raber, E. Efficacy of Liquid and Foam Decontamination Technologies for Chemical Warfare Agents on Indoor Surfaces. *J. Hazard. Mater.* **2011**, *196*, 115−122.
(68) Wagner, G. W.; Procell, L. R.; Sorrick, D. C.; Lawson, G. E.; Wells, C. M.; Reynolds, C. M.; Ringelberg, D. B.; Foley, K. L.; Lumetta, G. J.; Blanchard, D. L. All-Weather Hydrogen Peroxide-Based Decontamination of CBRN Contaminants. *Ind. Eng. Chem. Res.* **2010**, *49*, 3099−3105.

DOI: 10.1021/acsami.5b06905
ACS Appl. Mater. Interfaces 2015, 7, 22001−22011