Polymer-Bound 4-Pyridyl-5-hydroxyethyl-thiazole Fluorescent Chemosensors for the Detection of Organophosphate Nerve Agent Simulants

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ABSTRACT: Fluorescent sensors have been synthesized for organophosphate nerve agent detection. The resulting 4-pyridyl-5-hydroxyethyl structures react with organophosphate nerve agent simulants such as diethylchlorophosphate and diisopropylfluorophosphate and cyclize to form a dihydroquinolizinium ring that results in an increased fluorescence response to long-wave UV excitation. These sensors have been functionalized with monomeric substitutions that allow for covalent incorporation into a polymer matrix for organophosphate detection to develop a fieldable sensor. In addition, inclusion of silicon dioxide into the polymer matrix eliminated false-positive responses from mineral acids, greatly advancing this class of sensors.

INTRODUCTION

For more than 70 years, organophosphate acetylcholinesterase inhibitors have been used as weapons of warfare.1–3 In addition, this class of compounds are among the most used pesticides.4 Given their extensive general use, and the threat posed by the continued use of organophosphate warfare agents, studies to develop methods for the selective detection of these molecules are warranted and timely.5,6

Recent advances in colorimetric or fluorescent detection using chemical-based sensors include rhodamine-based fluorophores,7–10 boron-dipyrromethene dyes,11–15 and other similar strategies for the modifications of reactive and highly conjugated small-molecule probes.16–18 In some cases, reactivity-based selectivity has been utilized to differentiate between the detection of fluoro- or cyanophosphates.19 However, differentiation between common chemicals is difficult and false positives are a major concern in the practical use of fielded sensors. To date, none of these technologies have made their way into the field kits of chemical, biological, radiological, nuclear, and explosives responders.20,21

We have worked to improve upon the current state-of-the-art through continued study of the 2-pyridyl-1,2-butenyl-4-ol systems.22,23 It was demonstrated that pyridines appended to a four-carbon side-chain with a terminal alcohol could be used for the detection of reactive phosphate esters. Restricted rotation and subsequent planarity was achieved in the synthesis of the pseudoaromatic metallo-1,2-enedithiolate 1, providing increased spatial probability of intramolecular coordination of the butanol by the pyridine, resulting in significant fluorescent and absorbance properties (Figure 1). Subsequent work by Swager and co-workers in 2003 demonstrated that these were general properties of 2-pyridyl-1,2-butenyl-4-ol systems such as compounds like 2.24,25 In 2013, a colorimetric assay using 2-pyridyl-1,2-butenyl-4-ol systems to control complexation with iron(II) was explored.26 These methods are specific for reactive phosphates, phosphinates, and phosphonates that contain chloro, fluoro, and cyano groups and allow for rapid detection of these esters both colorimetrically and fluorometrically at room temperature.

The following work seeks to implement the above technology toward a robust fieldable sensor. Generation of fully organic and affordable sensors of this class can pave a way toward subsequent immobilization in a polymer matrix to aid

Figure 1. Representative fluorescent sensors. The pyridyl-1,2-butenyl-4-ol structure is highlighted in blue.

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in overcoming problems associated with the acidic byproducts of organophosphate hydrolysis, as has been shown in the literature.14,22,27,28

The ethyl-hydroxy group preserves the highly nucleophilic nature toward phosphate esters due to its spatial proximity to the intramolecular pyridine ring. Additionally, a thiazole in conjugation to the pyridine ring is suspected to improve its basicity through resonance stabilization of the protonated form by 2−3 pKa units, resulting in greater reactivity.29 Following phosphorylation, the activated phosphate ester is proposed to act as a leaving group for dihydropyrolidinium ring closure as illustrated in Scheme 1. Once the dihydroquinolizinium ring structure is formed, a higher fluorescence yield is observed as a result of increased π overlap and forced planarity of the A, B, and C rings. These improvements bring increased pertinence of this strategy in organophosphate detection.

**RESULTS AND DISCUSSION**

**Synthesis of Thiazole Dyes.** Thiazole dyes 5a−g can be synthesized from 3-bromo-4-oxo-4-(pyridin-2-yl)butyl acetate, 3, and a thioamide as demonstrated in Scheme 2. Cyclization with 4-aryl-thioamides or thiourea gave the target thiazoles in modest yields. After the thiazole formation, facile saponification yields the product in five synthetic steps with an overall yield of 19−38%. In addition to p-substituted phenyl substituents at the thiazole C-2 position, a dimer molecule was made using 1,4-naphthalenedicarbothioamide, and following the same synthetic scheme 6e was synthesized. Thiazole 4a was acylated with acrylic acid to provide the monomer 4f. An additional monomer unit was prepared via a Heck coupling of 4d with ethylene to provide styrene 4g.

The practical utility of organophosphate sensors can be realized by their incorporation into polymer films, which are generated using acryloyl or styryl substituents for radical-initiated polymerization with styrene. Two of such monomers have been synthesized as shown in Scheme 3. Amino-acid coupling with N,N′-dicyclohexylcarbodiimide was achieved using acrylic acid to produce the acrylamide 5b.32 The phenyl bromide 5f is converted to the styryl thiazole 5g after reaction with ethylene using Heck conditions.33 Co-polymers afforded from these monomers limits may provide increased resistance of the sensor to acids and provides precedent for future incorporation into molecularly imprinted polymers (MIPs) to enhance phosphate ester selectivity.34 It also allows co-polymerization with additional monomers containing basic functional groups, such as (diisopropylamino)ethyl-methacrylate (DPAEMA). This not only may negate the deleterious effects of the acids in phosphate sensing but also allows for a direct route to preparation of the MIP.

**Fluorescent Properties of Thiazole Dyes.** Fluorescence emission was expected to increase dramatically after cyclization of the dihydroquinolizinium ring, the results of which for dyes 5a−5g and 6a−6g are summarized in Table 1. For most dyes, the maximum excitation wavelength provided by emission scans was near 350 nm; however, that wavelength cannot be used for emission in testing due to native emission interference by organophosphoryl halides, such as diethylchlorophosphate (DECP) and diisopropylfluorophosphate (DFP), at excitation wavelengths of less than 375 nm. At an excitation wavelength of 355 nm, relative to 9,10-diphenylanthracene.

### Table 1. Absorbance and Emissive Properties of Thiazole Sensors

| dye | abs max λ | em. max λ<sub>em</sub> | ε<sup>a</sup> | ϕ<sup>b</sup> (%) |
|-----|------------|-------------------------|----------|-----------------|
| 5a  | 306        | 449                     | 5718     | 0.50            |
| 5b  | 296        | 450                     | 18 480   | 3.6             |
| 5c  | 298        | 449                     | 20 757   | 2.3             |
| 5d  | 300        | 453                     | 6767     | 2.1             |
| 5e  | 349        | 440                     | 16 693   | 11              |
| 6a  | 380        | 469                     | 2201     | 0.31            |
| 6b  | 360        | 471                     | 6767     | 15              |
| 6c  | 355        | 473                     | 5190     | 9.5             |
| 6d  | 357        | 473                     | 4955     | 11              |
| 6e  | 353        | 459                     | 25 795   | 4.6             |

<sup>a</sup>Recorded in chloroform at 395 nm. <sup>b</sup>Obtained in ethanol at λ<sub>exc</sub> = 355 nm, relative to 9,10-diphenylanthracene.
of 395 nm, DECP and DFP have no fluorescence emission and a significant emission response from the sensors remained apparent; therefore, 395 nm was chosen for dye comparison throughout the experiment. Another advantage of choosing an excitation wavelength above 375 nm is that the precursor alcohols absorb very little light at those wavelengths, resulting in a much reduced emission response for those starting materials and their HCl or HF salts. Synthesis of the dihydroquinolizinium derivatives 6a–6h using thionyl chloride provided purified reference standards for each compound that were characterized alongside their precursor alcohols (Table 1).

Calculation of fluorescent quantum efficiencies in comparison to 9,10-diphenylanthracene as a standard revealed trends among the thiazole dyes tested. For the 2-amino-thiazole 5a, the quantum efficiency did not change dramatically as expected. The rise in fluorescence emission at λ_{exit} = 395 nm is a direct result of greater absorbance by the fluorophore 6a at longer wavelengths. For the bis-naphthalene compound 1e, cyclization significantly reduced the quantum yield. For thiazoles 5b–5d, the opposite effect is observed where quantum efficiency is significantly increased after cyclization. The 4-halogen-substituted 2-phenylthiazoles exhibited lower quantum efficiencies in comparison to the 2-phenylthiazole 5b.

The π-systems of the thiazole and pyridine rings are forced into a plane upon cyclization, resulting in a maximum absorbance at a longer wavelength for all dyes. As a result, excitation at a wavelength of 395 nm provides an increase in fluorescence emission intensity, as shown in Figure 2. Quantum efficiencies were obtained for all dihydroquinolizinium derivatives and their respective alcohols. Although quantum efficiencies typically decreased after cyclization, the increase in the absorbance at longer wavelengths provided a striking difference in fluorescence intensity for the 395 nm excitation wavelength and for the 365 nm excitation wavelength typical of a longwave UV blacklight.

The increase in π-conjugation was expected to enhance quantum efficiency, so the opposite observation for 5e and 6e was surprising. A possible explanation is that steric effects cause the 2-phenyl or 2-naphthyl structures to be out of the plane of the thiazole π-system. Molecular mechanics calculations have been used to predict rotational barriers in fluorescence applications, and simple calculations revealed higher conformational energies for structures where the torsion angle between the two rings was fixed at 0 or 180°. Shown in Table 2, the molecular mechanics derived energy difference between structures with planar constraints and those that are out-of-plane is greater for the bis-thiazole-naphthalene compound 6e in comparison to the 2-phenyl thiazole structure 6b. Although this is a likely explanation, other factors should be considered as well, such as self-quenching or different excitation states that come into play upon cyclization. 5e was not chosen for further study due to the impracticality of a "turn-off" sensor in comparison to the "turn-on" sensors 5a and 5b.

The newly synthesized thiazole dyes 5a–5e react with organophosphoryl halides, such as organophosphate nerve agent simulants DECP or DFP, as expected. The formation of 6a and 6b and subsequent increase in fluorescence emission was examined through the use of DECP in solution phase studies. As a control, hydrochloric acid was also added in the same concentration to show the relative sensitivity to mineral acid. Protonation of 1a by HCl results in comparable increase in fluorescence response to DECP after excitation at 365 nm as shown in Figures 3 and 4. At 395 nm excitation, a difference

![Figure 2. UV absorbance (left) and fluorescence (right) properties of 5a and 6a, 5b and 6b, and 5e and 6e (1.0 × 10^{-6} M) in methanol. Fluorescence observed for λ_{exit} = 395.](Image 407 to 446)

![Figure 3. Fluorescence emission titration of 5a (left) and 5b (right) in chloroform (1 × 10^{-4} M). Emission is visible after 2 h exposure to 1 × 10^{-3} M DIFP or HCl (λ_{ex} = 365 nm). Inset images are respective for fluorescence emission under a long wave UV lamp (λ_{ex} = 365 nm).](Image 494 to 535)
between DECP and HCl is visible due to the increased absorbance of the cyclized product 5a at longer wavelengths (Supporting Information (SI) Figure 1). The effect of HCl sensitivity is much reduced for 5b. For practical use in solution phase, 5b is a better sensor at 365 nm excitation not only due to greater fluorescence yield upon cyclization but also due to its relative improved contrast of DECP response when compared to the same amount of HCl.

Cyclization was further examined through an increase in fluorescent response over time. In a similar fashion to previous experiments, excess organophosphate was allowed to react with 5a in a solution over a period of 2 h. The fluorescence response at \( \lambda_{\text{em}} = 395 \text{ nm} \) was examined at various time points. Within a few minutes, the presence of organophosphate is evident; however, for complete cyclization to occur, incubation of 5a with DECP must be allowed to take >2 h as shown from the solution phase fluorimetry emission experiments. The data support that the reaction is pseudo-first order in nature.

Perhaps a more useful examination of the utility of 5a and 1c is through the determination of the limit of detection against organophosphates. Two hours of incubation of 5a and 5b was allowed for varying concentrations of DECP, and their fluorescence emission was examined at \( \lambda_{\text{em}} = 395 \text{ nm} \). Both dyes exhibit a minimum limit of detection at \( 1 \times 10^{-4} \text{ M} \) for a dye concentration of \( 1 \times 10^{-4} \text{ M} \), roughly 1 equiv of DECP. For 5 equiv DECP, or \( 1 \times 10^{-4} \text{ M} \) DECP, the fluorescence intensity reaches a large jump in intensity. At lower concentrations of the dye, fluorescence intensity begins to have diminishing returns at 1 equiv of organophosphoryl chloride, as a result of slower reaction times and reduced total fluorescence (SI Figure 2).

**Synthesis and Characterization of Polystyrene Film Sensors.** It remains a concern that mineral acids caused false positives with these sensors in the solution phase. Therefore, the incorporation of the thiazole dyes into polymer films was sought with the hopes that immobilization would deter acid vapor mixing, as well as provide an opportunity for an acid scavenger to be present for increased sensitivity for electrophiles. Previously, organophosphate sensors have been distributed in triethylcitrate/cellulose acetate or RTV118 silicon films that were not optimized to reduce acid sensitivity.\(^{22,25}\) However, the incorporation of covalently bonded sensors as part of a polystyrene matrix was a focus of this work.

Two monomers were synthesized for incorporation into a polystyrene film, as shown in Scheme 3. Polymers were made using freshly purified styrene, monomers 5f or 5g, and catalytic azobisobutyronitrile (AIBN). To address the acid problem, varying percentages of DPAEMA were added. As a technique for solution phase sensing, a filter paper was coated with 2 mL of a 20% polymer (w/v) in either chloroform or toluene. Once dried, the coated filter paper was cut into 16 mm diameter circles using a hole punch, and analytes were added to test organophosphoryl halide and organophosphate pesticide detection (SI Figure 3). The DPAEMA-incorporated polymers did not differentiate from false positives as expected. It was not intuitive that HCl would be visible in all concentrations of basic monomer tested, and despite that, incorporation of the basic monomer proved unhelpful as sensitivity to DECP was decreased in films with higher concentrations (SI Figure 4). These results led to the abandonment of using DPAEMA as a strategy to solve the acid sensitivity issue.

To buffer acid response without the use of an incorporated organic base, silica gel was added to the diluted polymer solution before coating the filter paper to ensure a uniform dispersion as has been shown in other films with CsCO\(_3\).\(^{28,37}\) It was found that silica gel was effective at eliminating the response of the polymer to acid at 1 M concentrations, yet retained the response to DECP and even increased the fluorescence yield of DFP sensing. These results are summarized in Figure 5.

![Figure 4](image.png)

**Figure 4.** Time course for the fluorescence emission of 5a in chloroform \( (10 \times 10^{-4} \text{ M}) \) with DECP \( (10 \times 10^{-4} \text{ M}) \). Left: full emission scans from \( T = 0 \) to 120 min at \( \lambda_{\text{exc}} = 395 \text{ nm} \). Right: emission curve at \( \lambda_{\text{em}} = 515 \text{ nm} \).

**Figure 5.** Emission spectra at \( \lambda_{\text{exc}} = 395 \text{ nm} \) for SiO\(_2\) dispersed 0.1% 5f polystyrene polymer coated on filter paper with DECP, DFP, and HCl (1 M). Overlaid is the longwave UV fluorescence response at 365 nm to organophosphate exposure and 1 N HCl in methanol on silica-gel-infused filter paper test circles.

To examine vapor-phase organophosphate sensing, the 0.1% 5f in styrene polymer was spread over a quartz slide and allowed to incubate in a 20 mL sealed vial that contained 1 \( \mu \text{L} \) DECP at room temperature. The quartz slide was fitted in a fluorimetry cuvette and examined for fluorescence emission at \( 395 \text{ nm} \) at 5 and 10 min time points (SI Figure 5). In similar fashion, the polymer-dispersed filter paper circles were also exposed to DECP and DFP vapors, providing a positive response.

**CONCLUSIONS**

These results demonstrate a more practical use of 2-pyridyl-1,2-butenyl-4-ol organophosphate sensors than in solution phase. Alleviating acid contamination through the use of dispersed silicon dioxide is a step toward making a robust device that could be used in a variety of applications. The ability to use the sensors as polymer films provides a versatile
solvent-free platform for both vapor phase and direct drop-testing of unknown samples on a test strip to screen for organophosphoryl halide contamination. Further optimization of the polymers, such as use in a MIP, may allow for further differentiation between compounds of interest.

## EXPERIMENTAL SECTION

### Materials and General Methods.

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III-HD 400 MHz spectrometer (Bruker, Billerica, MA). $^{13}$C NMR spectra were obtained at 100 MHz using a proton-decoupled pulse sequence and are tabulated by observed peak. CDCl$_3$ (Oakwood Chemical, Estill, SC) or CD$_3$OD (Sigma-Aldrich, St. Louis, MO) were used as NMR solvents. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard, δ $^1$H/$^{13}$C (solvent): 7.26/77.00 (CDCl$_3$); 3.30/49.00 (CD$_3$OD); and are tabulated as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet), coupling constants, (J) in hertz (Hz), and number of protons. High-resolution electrospray ionization mass spectra were obtained on a LCQ Orbitrap Velos (ThermoFisher Scientific, Waltham, MA). UV–vis spectra were recorded at room temperature on a Cary 5000 UV−vis spectrophotometer (Varian, Palo Alto, CA). Solution phase emission and excitation spectra were obtained at room temperature using a Spex FluoroMax-2 Spectrofluorometer (Horiba Scientific, Edison, NJ). Solid-phase emission and excitation spectra were obtained at room temperature using an Infinite M1000 microplate reader (Tecan, Morrisville, NC) using 24-well corning cell culture plates painted with black with matte low-reflectance camouflage spray paint. Thin-layer chromatography was performed on ready-to-use glass-backed silica gel 60 plates (Sigma-Aldrich, St. Louis, MO). Flash column chromatography was performed over Acros silica gel (40–60 μm, 200–400 mesh). All the reactions were performed under an inert atmosphere of either Zero-grade nitrogen or argon (Airgas, Radnor, PA). All the chemicals were obtained from Sigma-Aldrich (St. Louis, MO), Fisher Scientific (Pittsburgh, PA), or Oakwood Chemicals (Estill, SC) and used without further purification.

### Synthesis of Compounds 1a−g−6a−g.

1-(2-Pyridyl)-2-bromo-4-acetoxybutan-1-one 3 was prepared according to the literature procedure. Further details and spectral data for the synthesis of these analogues and their synthetic intermediates are provided in the Supporting Information.

### General Procedure for the Polymerization of Polystyrene Films.

To benzene (5 mL) in a 30 mL vial fitted with a stir bar was added 2 mL styrene that had been passed through a column of inhibitor remover resin. To this was added monomers 4a or 4e with 0, 1, 5, or 10% v/v (diisopropylamino)ethyl-methacrylate (DPAEMA). A catalytic amount of azobisisobutyronitrile (AIBN) was added. The filled vial was fitted to a Schlenk manifold and placed under an atmosphere of argon. The reaction mixture was cooled in liquid nitrogen, evacuated with vacuum and warmed under static vacuum to degas the solution. This freeze−pump−thaw process was completed twice more before the vial was sealed under gentle heating of the neck with a propane torch under static vacuum. The sealed vial was stirred and heated to 75 °C for 16 h. After this time, polymerization was complete and the film cast and dried.

### Analysis of Solution Phase Fluorimetry Response of Thiazole Dyes to Organophosphates.

Thiazoles 5a, 5b, 5c, 5d, and 5e were analyzed for their fluorescence emission after incubation with organophosphate nerve agent simulating diethylchlorophosphate (DECP) or diisopropylfluorophosphate (DFP). The dyes were dissolved in either methanol or chloroform to a final concentration of 1 × 10⁻⁶ or 1 × 10⁻⁷ M, respectively. Three milliliters of diluted solution was pipetted into a 1.0 × 1.0 cm² quartz fluorimetry cell with clear walls on all four sides, capped, and the cuvette was placed into the Fluoromax-2 spectrophotometer and the door fully sealed. Analysis was performed at either 355 or 395 nm excitation wavelengths, and the emission spectra were scanned from 410 to 650 nm at a rate of 5 scans per second. The spectral bandpass was set to 5 nm for both the excitation and emission. A desired amount of simulant is added directly to the cuvette for additional testing, and a stir bar is fitted to the cuvette for facile mixing on an external magnetic stir plate. The polymer films were analyzed for their base and postexposure response by coating a small flat quartz insert with polystyrene films by drop-casting using a concentrated suspension of polymer in chloroform. The insert was placed at a 45° angle to the excitation beam, allowing for the detection of the fluorescence emission by the detector.

### Production of Polymer Film-Coated Filter Paper Test Strips and Testing.

Polystyrene films were concentrated to dryness in vacuo and suspended in chloroform (5 mL/g). Silica gel, alumina, or fumed silica was suspended into the solution (50 mg/2 mL). The films were coated onto 85 mm diameter qualitative fast-flow filter paper (2 mL solution) and allowed to dry. For uniformity, a 16 mm diameter circular hole-punch was used to cut out circular filter paper samples. These test circles were exposed to analytes directly. For complete coating, at least 40 μL was used to produce a uniform fluorescent response. Once dried, the test circles were placed into the bottom of a well in a matte black-painted 24-well microplate and analyzed for their fluorescent response at λ_exil = 395 using a microplate reader. Analysis was performed at either 355 or 395 nm excitation wavelengths, and the emission spectra were scanned from 365 to 750 or 410 to 750 nm, with a scan frequency of every 2 nm. The excitation band width was set to 5 nm. Gain was optimized for the well that contained the highest expected fluorescence to be analyzed.

### Calculation of Quantum Yields.

Quantum yields in ethanol were calculated from a standard curve for samples at concentrations of 0.2 × 10⁻⁵, 0.4 × 10⁻⁵, 0.6 × 10⁻⁵, 0.8 × 10⁻⁵, and 1.0 × 10⁻⁵ M for 5a, 6a, 5b, 5c, and 5d, and 0.2 × 10⁻⁶, 0.4 × 10⁻⁶, 0.6 × 10⁻⁶, 0.8 × 10⁻⁶ and 1.0 × 10⁻⁶ M for 6b, 6c, 6d, 5e and 6e, respectively. A volume of 200 μL was placed in each respective well in a 96-well clear or black polystyrene flat-bottom microplate (Corning, Tewksbury, MA). Both the absorbance at 355 nm and the total integrated fluorescence at λ_exil = 355 were plotted for each compound. Using the literature quantum efficiency value of 0.95 for 9,10-diphenylanthracene in ethanol, the resulting slopes from fluorescence over absorbance were compared to that generated for the fluorescence standard at concentrations of 0.2 × 10⁻⁷, 0.4 × 10⁻⁷, 0.6 × 10⁻⁷, 0.8 × 10⁻⁷, and 1.0 × 10⁻⁷ M. Total integrated fluorescence was calculated using the following formula for integration of a manual plot:

\[
\int_0^\infty y(x) \, dx = \frac{(b-a)}{N} \sum_0^N y(x), \text{ where } a = 365 \text{ nm, } b = 749 \text{ nm, and } N = 192.
\]

### Computational Details.

Molecular mechanics (MMFF94) calculations were performed using Spartan'16
V2.07 (Wavefunction, Irvine, CA). Conformational structures for 5b, 5e, 6b, and 6e were minimized using this function and associated energies calculated and recorded for the minimum-energy conformation. For these structures, the torsion angle was examined between C2 of the thiazole ring and the phenyl ring of 5b and 6b or napthyl ring of 5e and 6e, respectively (Table 2). The calculations were repeated for each structure after constraining this torsion angle at 0 or 180°, and the respective energies are tabulated for comparison.

### ASSOCIATED CONTENT

1. Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02313.

- Experimental procedures and characterization; synthesis of polystyrene films; procedure for filter paper coating, exposure and measurements; NMR spectra for synthesized compounds (PDF)

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**Author Contributions**

E.P.L. and K.A.V.H. designed the experiments, performed the chemical synthesis, characterization, and analysis, and wrote the manuscript. R.S.P. designed the experiments, performed the chemical synthesis, and reviewed the manuscript.

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### ABBREVIATIONS

- DPAEMA, (diisopropylamino)ethyl-methacrylate; AIBN, azobisisobutyronitrile; DECP, diethylchlorophosphate; DFP, diisopropylfluorophosphate; MIP, molecularly imprinted polymer

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