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Thiophene-fused Tropones as Chemical Warfare Agent-Responsive Building Blocks

Jonathan G. Weis and Timothy M. Swager*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, United States

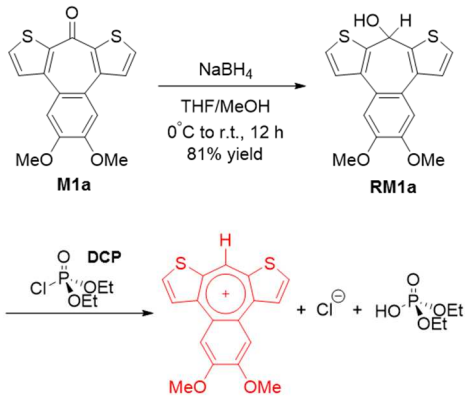
ABSTRACT: We report the synthesis of dithienobenzotropone-based conjugated alternating copolymers by direct arylation polycondensation. Post-polymerization modification by hydride reduction yields cross-conjugated, reactive hydroxyl-containing copolymers that undergo phosphorylation and ionization upon exposure to the chemical warfare agent mimic diethylchlorophosphate (DCP). The resulting conjugated, cationic copolymer is highly colored and facilitates the spectroscopic and colorimetric detection of DCP in both solution and thin-film measurements.

Electrophilic organophosphates are the basis of many chemical warfare agents (CWAs) and pesticides and derive their high toxicity from their capacity to inhibit acetylcholinesterase (AChE) by phosphorylating the active site of the enzyme. The threat of CWAs against military and civilian targets necessitates detection schemes that are operationally simple, sensitive, portable, and cost-effective.

Techniques used to detect organophosphorus CWAs include mass spectroscopy,[1,2] electrochemical sensors,[3,4] microelectromechanical systems,[5,6] chemiresistors,[7] and fluorescent indicators.[8,9] Colorimetric sensors are attractive as a result of their excellent operational simplicity, portability, and ability to integrate functionality that reacts with CWAs. Colorimetric schemes have been reported with reactive aldehydes,[10] alcohols,[11–16] oximes,[17–20] and amines.[21]

Although many solution-based colorimetric detection schemes have been reported, there are far fewer examples with colorimetric responses in thin films, which is necessary for the real-time detection of organophosphates. Most previous approaches to CWA colorimetric thin film sensing involve embedding chromogenic small molecules into a polymer matrix.[15,22] An attractive alternative is the covalent attachment or direct incorporation of chromophores into polymers.[18] This strategy can greatly increase the robustness of these materials and enable stimuli-responsive materials that undergo bulk electronic and mechanical changes in response to CWAs.

Inspired by the triarylmethanol-containing chromophores reported by Gotor et al.,[15] and our group's successful synthesis of dithienobenzotropone **M1a**,[23] we postulated that reduction of a dithienobenzotropone-containing polymer would result in reactive alcohols that could function as CWA indicators. As a result of the fused, electron-donating thiophene and dialkoxybenzene rings, the phosphorylated alcohol readily ionizes to form a highly resonance-stabilized and colored tropylium cation, realizing colorimetric and spectroscopic detection (Scheme 1).



Scheme 1. Synthesis of CWA-reactive **RM1a** and ionization with CWA mimic diethylchlorophosphate.

The dithienobenzotropone monomer **M1a** (Scheme 1) can be constructed in five steps from the appropriate *o*-dialkoxybenzene.[23] To incorporate this moiety into a polymer, we chose direct arylation polycondensation, which circumvents the need to prefunctionalize one of the monomers and evades the stoichiometric formation of toxic, organotin byproducts.[24,25] In addition, we report the reduction of these polymers to CWA simulant-reactive alcohols. Upon exposure to nerve agent simulant diethylchlorophosphate (DCP), these polymers undergo drastic spectroscopic and colorimetric changes in solution and thin-film measurements. Furthermore, we demonstrate that the inclusion of hydrogel-promoting side chains significantly enhances the response of these polymers to DCP in thin films.

Synthesis of CWA Simulant-Reactive Monomers. To examine the reactivity of the 8*H*-benzo[6,7]cyclohepta[2,1-*b*:4,5-*b*']dithiophen-8-ol unit, we first synthesized reduced

derivatives of our monomers for direct arylation. Dimethoxy-substituted dithienobenzotropone **M1a** (Scheme 1) was synthesized from veratrole according to a procedure reported by our group,[23,26,27] and tropones **M1b** and **M1c** were synthesized using an analogous synthesis starting from the corresponding *o*-dialkoxybenzenes (Scheme S1).

We synthesized the reactive alcohol as shown in Scheme 1, by reducing tropone **M1a** to alcohol **RM1a** using sodium borohydride in a tetrahydrofuran/methanol (4:1) solution at room temperature in 81% yield. We also synthesized regioisomer **RM2a** using a similar synthetic route starting from 4,5-di-(2-thienyl)-veratrole (Scheme S2).

Responses to CWA Mimic DCP. Diethylchlorophosphate is often used as a nerve agent simulant in the development of CWA detection schemes as a result of its similar electrophilic reactivity and lower relative toxicity than actual nerve agents (e.g. Sarin, Soman, Tabun).[12,13,16,28] These organophosphorus CWA simulants are known to degrade to acidic products over time,[14] and to prevent interference (false positives) from strong acid, we syringe-filtered a 1M DCP solution in dichloromethane through a pad of dry potassium carbonate before each sensing experiment. To evaluate the response of alcohol **RM1a** to DCP, we exposed a 5 μM solution of **RM1a** in dry dichloromethane to DCP at a concentration of 40 ppm. The UV–Vis absorption spectrum exhibited a strong bathochromic shift of λ_{onset} from 330 nm to 580 nm (Figure 1a), and comparison of the proton NMR spectra of alcohol **RM1a** and the resulting cation reveals a downfield shift of the proton labeled H_a in Figure 1 from δ 5.87 to δ 9.65, as a result of aromatic ring currents and deshielding caused by ionization (Figure S1). Both of these observations and the change in color from colorless to fuschia (Figures 1b and 1c) are consistent with the formation of the aromatic dithienobenzotropylium cation.

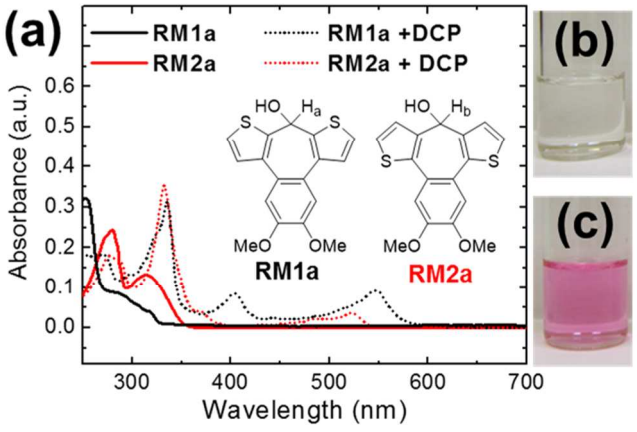


Figure 1. (a) UV–Vis absorption spectra of 5 μM solutions of monomers **RM1a** (black) and **RM2a** (red) in CH_2Cl_2 before (solid) and after (dotted) exposure to 40 ppm DCP. Photographs of **RM1a** in CH_2Cl_2 before (b) and after (c) addition of DCP.

Spectroscopic and colorimetric comparison of monomers **RM1a** and **RM2a** led us to pursue polymers containing the 3-thienyl-derived regiomeric structure of **RM1a** that provides intense color change and greater bathochromic shift as compared to the 2-thienyl **RM2a** (Figure 1a). Nonetheless, alcohol **RM2a** undergoes phosphorylation and ionization to yield the resulting tropylium cation, with a bathochromic shift in the absorption spectra (Figure 1a) and a downfield shift in the NMR spectra of proton H_b from δ 5.39 to δ 9.65 (Figure S2). Similar to the hydride reduction, the tropone can be converted into a reactive alcohol by addition of an aryllithium to create a readily ionizable compound (Scheme S3). To evaluate these different constructs, we performed comparative kinetics for the reaction of the respective tertiary and secondary alcohols with DCP, as determined by UV–Vis spectroscopy (Figure S3). The addition of a phenyl group resulted in a 100-fold decrease in the pseudo-first-order rate constant compared to that of the secondary alcohol created by hydride reduction. We attribute this decrease to the increased steric demand of the phenyl adduct in the phosphorylation step. It is important to note that the addition of an aromatic ring does not significantly alter the electronic transitions or chromaticity of the tropylium cation formed upon reacting with the nerve agent simulant. Density functional theory (DFT) calculations (B3LYP/6–31G*) of the tropylium cations suggest that the aromatic ring is oriented nearly perpendicular to the tropylium ring (Figure S4). This calculation is in agreement with the observation that there is no significant change in the absorption spectra for different phenyl adducts having para electron-donating and -withdrawing groups (Figures S5a–c). Similarly, we evaluated the butyl adduct and find no significant alteration of the absorption spectrum or color of the resulting cation, in comparison to that of hydride adduct **RM1a** (Figure S5d). The fully substituted tropylium cations have indefinite stability in ambient conditions; however, those generated from the secondary alcohols began to generate traces of tropone products after a few hours in solution. In this case, we expect that the carbocations, with some secondary alcohols, undergo hydrogen atom abstraction reactions that generate the tropones.

We demonstrated that the CWA-responsive monomer can be regenerated from the tropylium cation by washing the cation with a 1M aqueous solution of sodium hydroxide. A change in color from fuschia to colorless was observed (Figure S6), and UV–Vis absorption measurements confirm the regeneration of alcohol **RM1a**.

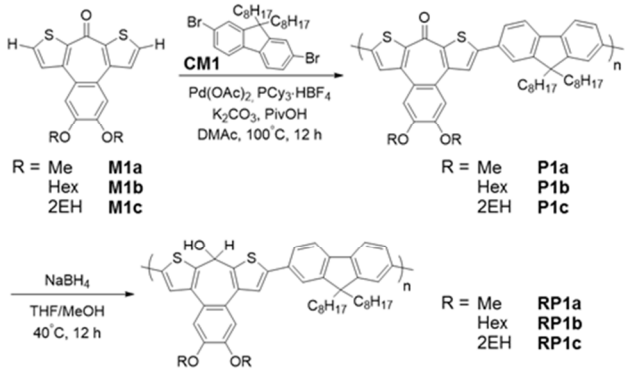
Polymer Synthesis by Direct Arylation Polycondensation. The bromination or iodination at the alpha positions of the thiophenes in compounds **M1b** and **M1c** proved difficult and proceeded in low yields (<17 %), consistent with previous efforts in iodinating compound **M1a**.[23] Additionally, attempts to copolymerize these compounds by Stille coupling with 5,5′-bis(tributylstannyl)-2,2′-bithiophene yielded only oligomers.

Consequently, we chose an alternative, direct arylation polycondensation, in order to circumvent the current chemical limitations imposed by **M1a–c**. As mentioned earlier, this step-growth polymerization C–H activation strategy also eliminates toxic byproducts associated with Stille couplings and is fundamentally more atom econom-

ical. Our initial investigations with Herrmann's catalyst,[29] tris(o-anisyl)phosphine, and cesium carbonate in tetrahydrofuran at 120°C resulted in the successful polymerization of regioisomers **M1a** and **M2a** with comonomer 2,7-dibromo-9,9-dioctylfluorene (**CM1**). Although the polymers were isolated in high yields (>90%), the molecular weights obtained by gel permeation chromatography (GPC) were low for the THF-soluble fractions (< 2.50 kDa), which suggests that the polymerization may be limited by solubility.

To create higher molecular weight materials, we synthesized monomers **M1b** and **M1c**, with solubilizing hexyloxy and 2-ethylhexyloxy groups, respectively, for increased solubility to enable the screening of additional conditions for direct arylation polycondensation. We ultimately found the previously reported conditions[30,31] of $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, pivalic acid, and K_2CO_3 in dimethylacetamide at 100°C for 12 hours to be the optimized reaction conditions. Higher molecular weights were obtained, although polymers **P1b** (Mn=6.20 kDa, PDI=1.98) and **P1c** (Mn=7.60 kDa, PDI=2.61) remained only moderately soluble in organic solvents, despite the inclusion of two solubilizing 2-ethylhexyl chains in **P1c**.

To obtain CWA-responsive polymers, we reduced polymers **P1b** and **P1c** to polymers **RP1b** and **RP1c**, respectively, using sodium borohydride at 40°C in tetrahydrofuran/methanol (4:1) (Scheme 2). The resulting alcohol-containing polymers exhibited markedly improved solubility in organic solvents, and the UV–Vis and fluorescence spectra (Figure S7) reveal hypsochromic shifts upon reduction, which is expected considering the conversion from highly delocalized dithienobenzotropone-containing polymer **P1c** to the reduced, cross-conjugated polymer **RP1c**.



Scheme 2. Direct arylation polycondensation of monomers **M1a–c** and 9,9-dioctyl-2,7-dibromofluorene (**CM1**) to polymers **P1a–c** and their subsequent reduction to **RP1a–c**.

Various other copolymers were targeted from **P1c**, specifically those replacing the fluorene comonomer unit with a thiophene or bithiophene (Schemes S4, S5). The increased donor–acceptor character between the tropylium cation and electron-rich bithiophenes in particular resulted in large red shifts of greater than 50 nm in the absorption spectra (Figure S8) in comparison to the resulting polymer with the fluorene-based comonomer. Unfortunately, limited solubility for both the parent and reduced bithiophene-containing polymers prevented further characterization.

Polymer Response to DCP. To examine the polymers' response to DCP in solution, we exposed a 5 μg/mL solution of **RP1c** in dichloromethane to 40 ppm DCP. We chose **RP1c** as a result of its increased solubility in comparison to **RP1a** and **RP1b**. The UV–Vis absorption spectrum displayed a strong, bathochromic shift upon exposure to DCP, shifting the absorption onset from 480 nm in **RP1c** to 784 nm (Figure 2a). This process functions well as a colorimetric detection scheme, with an immediate change in color from colorless to bright blue (Figures 2b and 2c). We also successfully regenerated the parent reduced material by washing the organic layer with 1M sodium hydroxide (Figure S9).

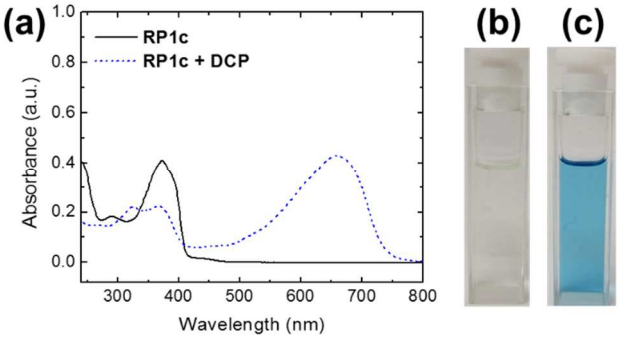
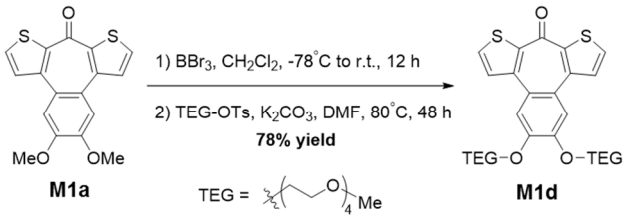


Figure 2. (a) UV–Vis absorption spectrum of a 5 μg/mL solution of polymer **RP1c** in CH_2Cl_2 (black, solid line) and after addition of DCP (blue, dashed line). Photographs of solution (b) before and (c) after addition of DCP.

To investigate thin film responses of **RP1b** and **RP1c**, we spin-coated the polymers onto glass microcover slides. This initial approach was unsuccessful, and we were unable to observe a response with saturated DCP vapor. A small spectroscopic response was observed when the polymer film was exposed to concentrated trifluoroacetic acid vapor, although we expected complete conversion under such extreme conditions. Consequently, we reasoned that the conjugated polymer thin film exhibits low permeability to the desired analytes. To rectify this limitation, we have targeted conjugated polymers with hydrogel-promoting tetra(ethylene glycol) monomethyl ether side chains to promote a more breathable material. This property was expected to facilitate percolation of the analyte into the membrane, giving rise to enhanced colorimetric and spectroscopic responses.[32]

Synthesis of TEG-Containing Monomer. The high polarity and diverse solubility of tetra(ethylene glycol)-containing dithienylbenzene precursors can present difficulties in purification of the different intermediates. To best prepare monomer **M1d**, we opted to add the polar groups at a late stage in the synthesis by modifying **M1a** through deprotection with boron tribromide and subsequent dialkylation with tetra(ethylene glycol) monomethyl ether tosylate with an overall yield of 78%, as shown in Scheme 3. It is important to note that the intermediate catechol is air-sensitive and insoluble in common organic solvents, and appropriate synthetic measures must be

followed to avoid its decomposition (see Supporting Information for details).



Scheme 3. Synthesis of tetra(ethylene glycol) monomethyl ether-substituted monomer **M1d** from monomer **M1a**.

Thin Film Response of Hydrogel Polymers to DCP. Direct arylation polycondensation of monomer **M1d** with dibromofluorene **CP1** yielded polymer **P1d** with an improved molecular weight of 12.2 kDa (PDI=1.90) determined by GPC relative to polymers **P1b** and **P1c**. We ascribe this increased molecular weight to the favorable solubilizing effect of the tetra(ethylene glycol) monomethyl ether side chains. Polymer **P1d** was subsequently reduced to polymer **RP1d** (Mn=16.6 kDa, PDI=1.91) with sodium borohydride. The discrepancy in the molecular weight can be attributed to a conformational change upon reduction and increased affinity for the tetrahydrofuran solvent. The nearly identical PDI values and unimodal distributions by GPC suggest that no degradation to the polymer backbone occurred.

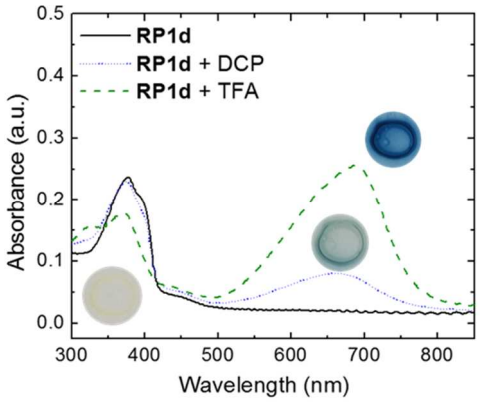


Figure 3. UV–Vis absorption spectrum of polymer **RP1d** as a thin film (a) before (black, solid line) and after exposure to saturated vapor of (b) DCP (blue, dotted line) and (c) TFA (green, dashed line).

Tetra(ethylene glycol) monomethyl ether-containing polymer **RP1d** behaves similarly to 2-ethylhexyl-containing polymer **RP1c** in its response to DCP and diisopropylfluorophosphate (DFP) in a solution of dichloromethane (Figures S10 and S12), undergoing a colorimetric change from faint yellow to bright blue and exhibiting a strong bathochromic shift in the absorption spectrum. Polymer **RP1d** has a detection limit of 6 ppm for DCP (Figure S11) and exhibits no response to possible interferents dimethyl methylphosphonate, pinacolyl methylphosphonate, and acetic acid (Figure S12).

Gratifyingly, thin films of polymer **RP1d** also gave strong colorimetric and spectroscopic responses to DCP vapor, as shown in Figure 3. This response is consistent with the increased breathability of the TEG-containing thin film to respond to the analyte, as compared to the nonresponsive 2-ethylhexyl-containing polymer. The thin-film response of polymer **RP1d** to trifluoroacetic acid vapor is also significantly enhanced (>200% of the response of **RP1c**). The thickness of the films of **RP1c** were approximately 50 nm and thinner films could enhance the response. However, it is also likely that the mechanical properties of the film are critical for diffusion. Polymer **RP1d** with its hydrogel-promoting components is sufficiently soft that thickness could not be measured by profilometry. The polymer dynamics in this case likely enhance diffusion into the polymer films.

Although we were able to successfully regenerate the active alcohol-containing polymers in solution by washing with basic aqueous solution, a vapor-phase regeneration is ideal for thin-films. With the improved breathability of the tetra(ethylene glycol)-containing polymer, we were able to successfully convert the cationic polymer back to the reactive cross-conjugated polymer by exposure to ammonium hydroxide vapor (Figure S13).

In conclusion, we have synthesized a cross-conjugated polymer that undergoes rapid phosphorylation and ionization to form an aromatic, conjugated polymer upon exposure to the CWA simulant DCP in solution and thin films. The resulting cationic copolymer is highly colored and enables the colorimetric and spectroscopic detection of the nerve agent simulant diethylchlorophosphate. Direct arylation polycondensation was essential to achieve sufficiently high molecular weights (>10 kDa), and the inclusion of hydrogel-promoting tetra(ethylene glycol) monomethyl ether side chains was critical to increasing the molecular weight and thin-film permeability of the polymer to the analyte. With the inclusion of a reactive moiety into the polymer backbone, we envision a class of stimuli-responsive materials that not only detect the presence of chemical threats, but also functionally respond by undergoing conformational changes that affect their physical properties.

ASSOCIATED CONTENT

Supporting Information. Synthesis of monomers and polymers. UV–Vis, fluorescence, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org/journal/amlccd.

AUTHOR INFORMATION

Corresponding Author

*Email: tswager@mit.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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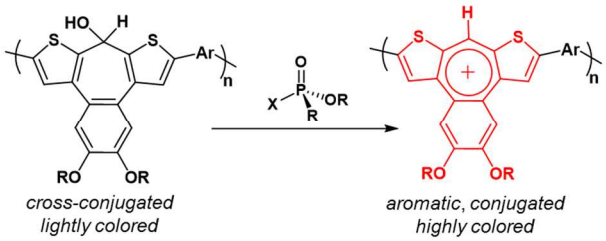

cross-conjugated lightly colored

aromatic, conjugated highly colored