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Functionalized Polythiophene Copolymers for Electronic Biomedical Devices

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ABSTRACT

We continue to investigate the design, synthesis, and characterization of electrically and ionically active conjugated polythiophene copolymers for integrating a variety of biomedical devices with living tissue. This paper will describe some of our most recent results, including the development of several new monomers that can tailor the surface chemistry, adhesion, and biointegration of these materials with neural cells. Our efforts have focused on copolymers of 3,4 ethylenedioxythiophene (EDOT), functionalized variants of EDOT (including EDOT-acid and the trifunctional EPh), and dopamine (DOPA). The resulting PEDOT-based copolymers have electrical, optical, mechanical, and adhesive properties that can be precisely tailored by fine tuning the chemical composition and structure. Here we present results on EDOT-dopamine bifunctional monomers and their corresponding polymers. We discuss the design and synthesis of an EDOT-cholesterol that combines the thiophene with a biological moiety known to exhibit surface-active behaviour. We will also introduce EDOT-aldehyde and EDOT-maleimide monomers and show how they can be used as the starting point for a wide variety of functionalized monomers and polymers.

INTRODUCTION:

Functionalized polythiophene copolymers based on alkyl-dithiophenes, particularly poly(3,4-ethylene dioxythiophene) (PEDOT) and poly(3,4-propylene dioxythiophene) (PProDOT), have shown considerable interest for electronic biomedical devices, organic photovoltaics, and chemical sensors [1][2]. PEDOT and PProDOT copolymers have excellent mechanical properties, thermal stability, and chemical stability, making them attractive for use in these applications. PEDOT doped with poly(4-styrene sulfonate) (PSS) is commercially available in a processable aqueous suspension for fabricating organic electronic devices at relatively large scale. We typically use electrochemical polymerization to deposit these materials directly onto a conducting electrode, making it possible to precisely control the process [3–4].

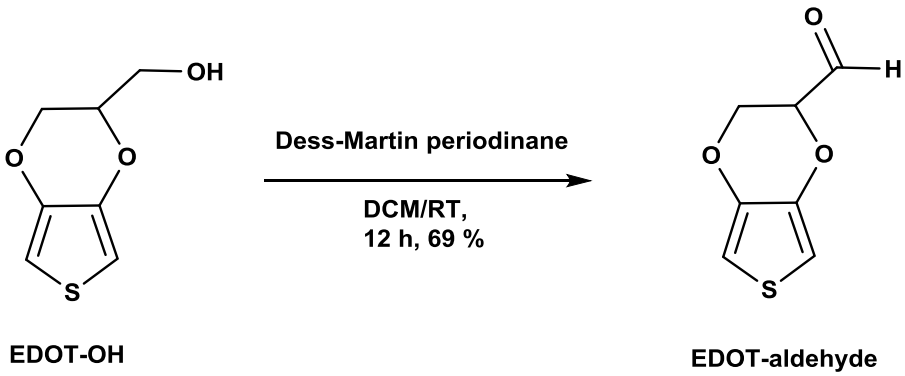
While PEDOT has shown considerable potential for these various applications, the polymer is relatively hydrophobic, and can show issues with relatively poor adhesion to solid surfaces. It also does not have any specific functionality for optimizing interactions with living tissue. This leads to issues in long-term performance, due to the possibility of cracking or delamination of the film, and unfavourable interactions with biological media [5].

A variety of research groups, including our own, have investigated the ability to create thiophene monomers with functionalized side groups. These materials can be polymerized to make entirely new polymers or can be copolymerized to make polymers with controlled, variable amounts of a desired chemistry. Examples include an azidomethyl-EDOT that was polymerized and post-functionalized with various alkynes using Cu+ click chemistry [6]. Thiol-ene click chemistry was used to attach a variety of side groups to polythiophenes [7–8]. Carboxylic acid side groups have also been described and used to attach peptides to surfaces and improve adhesion [9–11][12].

Here, we describe the design, synthesis, and characterization of a number of novel functionalized thiophene monomers that can be used to create the corresponding polythiophene derivatives. These new functionalities include aldehyde, maleimide, dopamine, tyramine, and cholesterol. The chemical structures of these compounds have been confirmed by FTIR, ^{13}C NMR, and ^{1}H NMR. Studies to fully characterize these materials using a variety of techniques including optical and electron microscopy, UV/Vis spectroscopy, cyclic voltammetry, electrochemical impedance spectroscopy, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) are ongoing.

EDOT-aldehyde

EDOT-aldehyde was synthesized starting from commercially available EDOT-OH by the route illustrated in Scheme 1.



Scheme 1: Synthesis of 2'-carbaldehyde-3,4-ethylenedioxythiophene (EDOT–aldehyde).

EDOT-aldehyde was characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H NMR spectra (Figure 1) revealed a signal at 9.77 δ ppm corresponding to aldehyde

carbonyl. Assignment of remaining protons is also depicted in Figure 1**;** the spectra agreed well with the proposed molecular structure of EDOT-aldehyde.

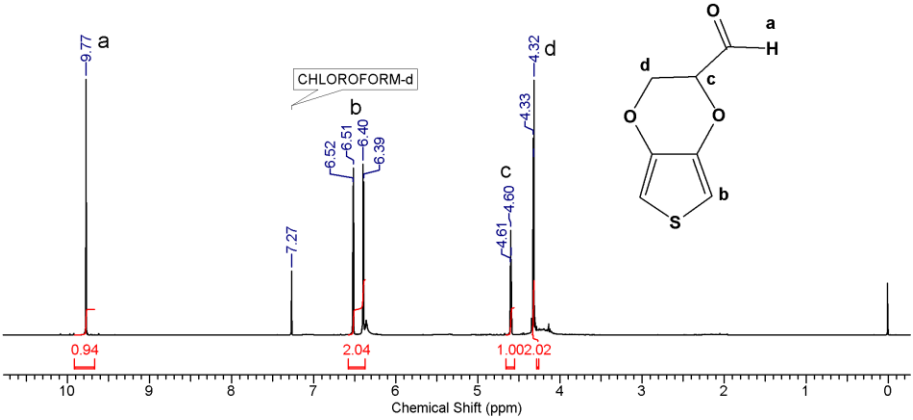
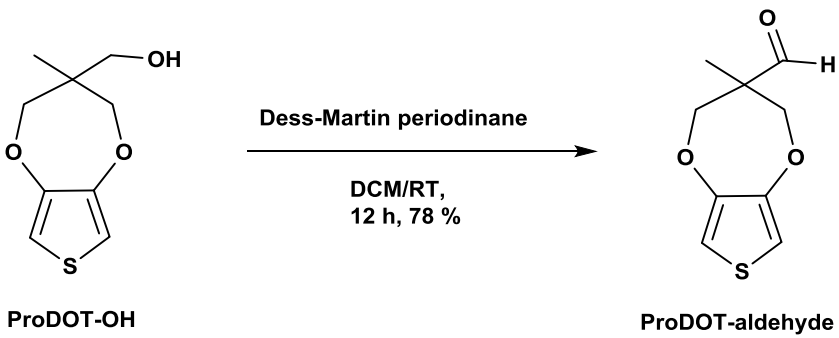


Figure 1. ^{1}H-NMR spectrum (in $CDCl_3$) of 2'-carbaldehyde-3,4-ethylenedioxythiophene (EDOT–aldehyde).

ProDOT-aldehyde

Scheme 2 represents the route followed for the synthesis of ProDOT-aldehyde starting from ProDOT-OH *via* a one-step reaction pathway.



ProDOT-OH **ProDOT-aldehyde**

Scheme 2: Synthesis of 3-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-3-carbaldehyde (ProDOT–aldehyde).

ProDOT-OH was synthesized by a reported procedure [13]. ProDOT-OH was reacted with Des-Martin periodinane in dry dichloromethane as a solvent at room temperature to obtain ProDOT-aldehyde. From the crude product, ProDOT-aldehyde was isolated by silica gel column chromatography with petroleum ether:ethyl acetate as an eluent and was characterized by FT-IR, ^{1}H NMR and ^{13}C NMR and spectroscopy. A ^{1}H NMR spectrum, along with peak assignments, of ProDOT-aldehyde is shown in Figure 2. The spectra were in good agreement with the proposed molecular structure of ProDOT-aldehyde.

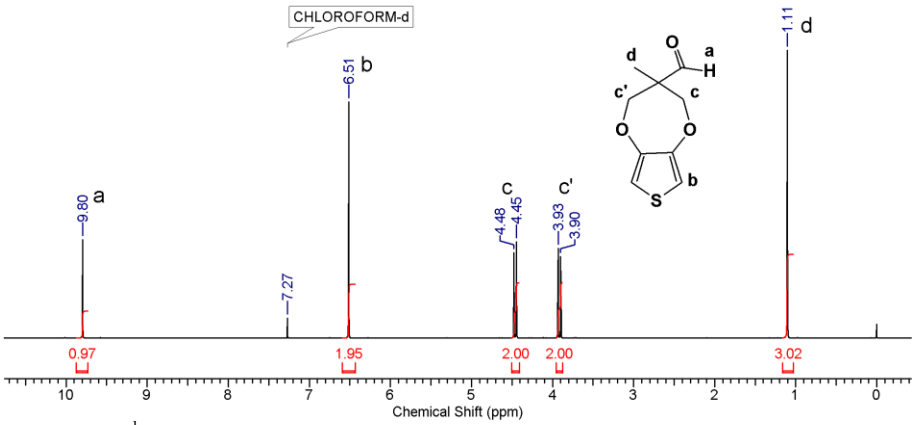
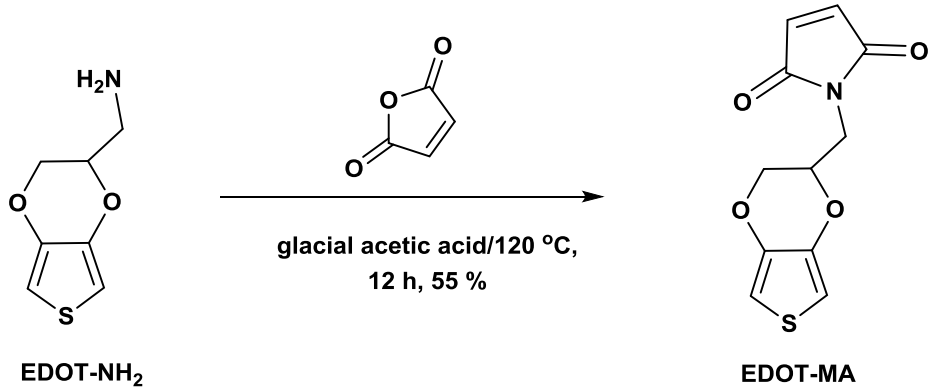


Figure 2. ^{1}H-NMR spectrum (in $CDCl_3$) of 3-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-3-carbaldehyde (ProDOT–aldehyde).

EDOT-maleimide



Scheme 3. Synthesis of 2'-maleimideomethyl-3,4-ethylenedioxythiophene (EDOT–MA).

Scheme 3 depicts the route followed for the synthesis of EDOT-maleimide (EDOT-MA) monomer starting from EDOT-NH_2. 3,4-dimethoxythiophene was converted into EDOT-NH_2 by the reported procedure [14]. EDOT-NH_2 was reacted with maleic anhydride in acetic acid to afford EDOT-MA.

Analysis data obtained from FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy was used to support the formation of EDOT-MA. The ^{1}H NMR spectrum of EDOT-MA is illustrated in Figure 3. The characteristic peak of the maelimide vinyl protons was observed at 6.77 δ ppm which indicated the successful synthesis of the EDOT containing maleimide group. The spectral data for other protons were in good agreement with the proposed structure.

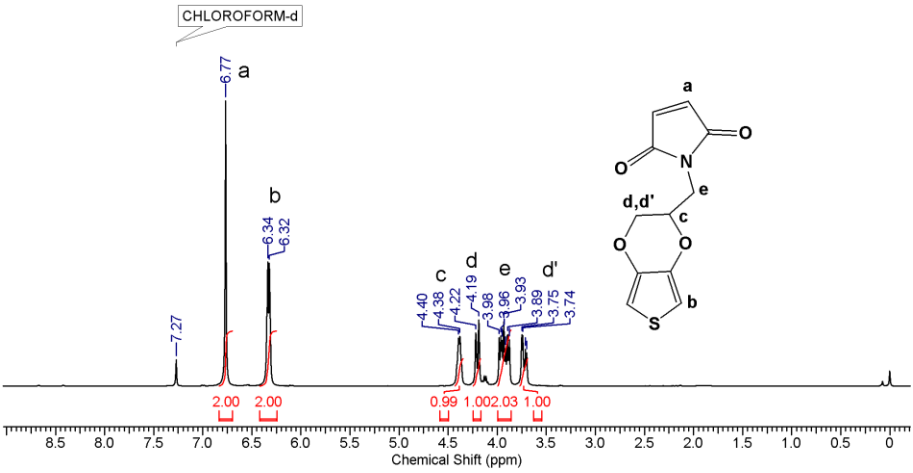
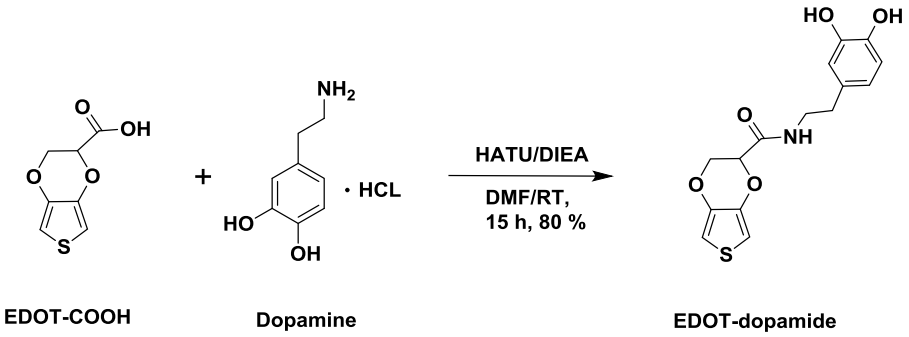


Figure 3. ^{1}H-NMR spectrum (in $CDCl_3$) of 2'-maleimideomethyl-3,4-ethylenedioxythiophene (EDOT–MA).

EDOT-dopamide

Scheme 4 outlines the synthesis of EDOT-dopamide by reaction of EDOT-acid with dopamine.



Scheme 4: Synthesis of N-(3,4-dihydroxyphenethyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-2-carboxamide (EDOT-dopamide).

EDOT monomer containing pendant phenols was readily synthesized in a one-step reaction by condensation of EDOT-acid with dopamine in the presence of DIPEA and HATU at room temperature. The crude product was purified by column chromatography to afford EDOT-dopamide. The chemical structure of EDOT-dopamide was confirmed by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H NMR spectra of EDOT-dopamide exhibited signals at 6.93 and 6.75 δ ppm which correspond to phenolic aromatic protons.

Assignment of remaining protons is depicted in Figure 4 and spectra agreed well with the proposed molecular structure of EDOT-dopamide.

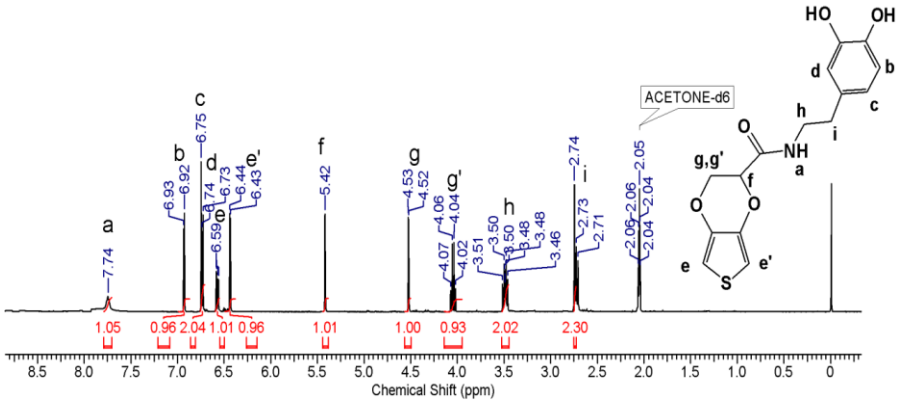
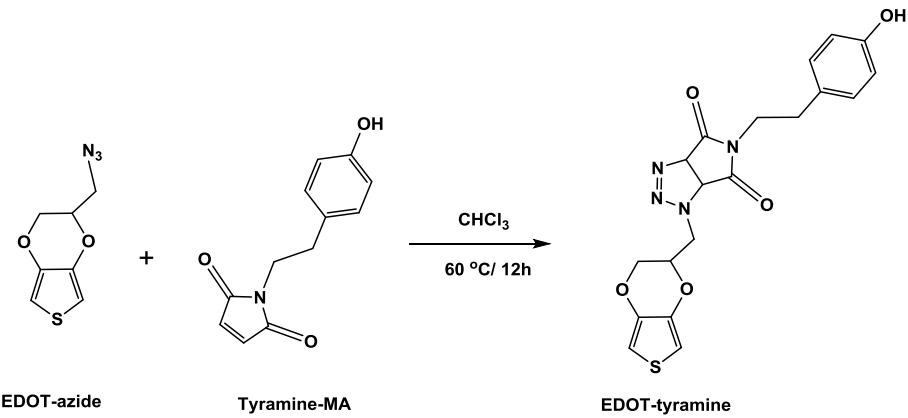


Figure 4. ^{1}H-NMR spectrum (in Acetone-d_6) of N-(3,4-dihydroxyphenethyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-2-carboxamide (EDOT-dopamide).

EDOT-tyramine

An EDOT containing tyramine was synthesized starting from EDOT-N_3 and tyramine-MA *via* metal-free 1, 3- dipolar azide-maleimide cycloaddition click reaction in dry chloroform at 60 ^{o}C for 12 h (**Scheme 5**).



Scheme 5: Synthesis of EDOT-tyramine.

The chemical structures of EDOT-tyramine was confirmed by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. A ^{1}H NMR spectrum of EDOT-tyramine, along with assignments of the protons, is shown in Figure 5.

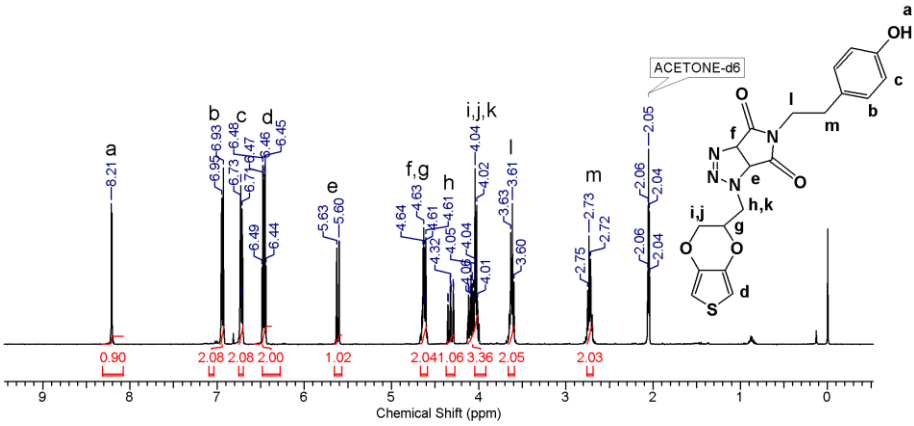
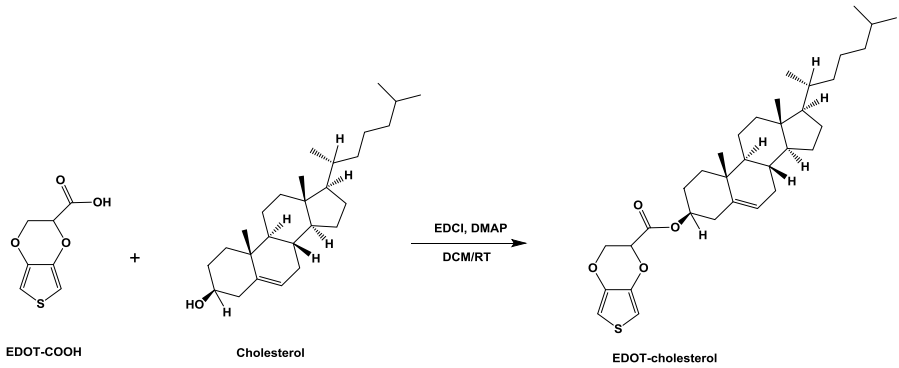


Figure 5. ^{1}H-NMR spectrum (in $CDCl_3$) of EDOT-tyramine.

EDOT-cholesterol

EDOT containing cholesterol was readily synthesized in a one-step reaction by condensation of EDOT-acid with cholesterol in the presence of EDCI and DMAP at room temperature. The crude product was purified by column chromatography to afford EDOT-cholesterol (Scheme 6).



Scheme 6: Synthesis of EDOT-cholesterol.

The chemical structures were elucidated on the basis of FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Assignment of protons is depicted in Figure 6 and the ^{1}H NMR spectra agreed well with proposed molecular structure of EDOT-cholesterol.

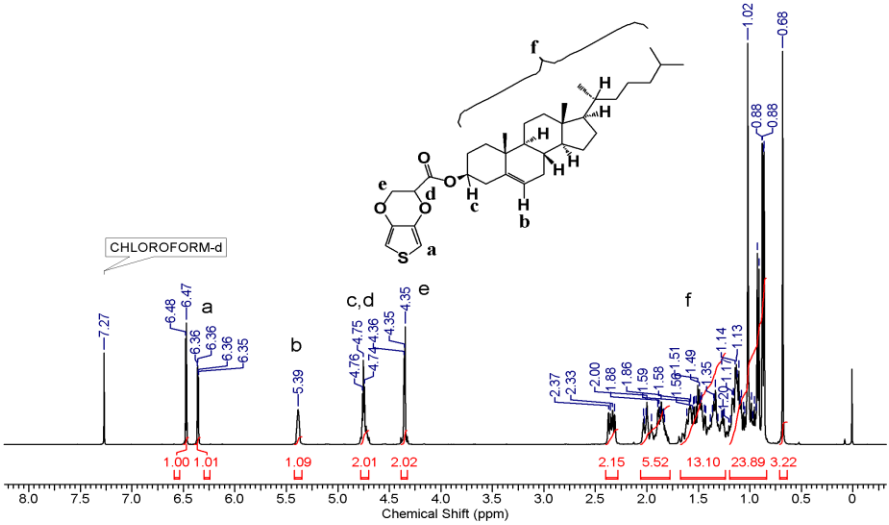


Figure 6. ^{1}H-NMR spectrum (in $CDCl_3$) of EDOT-cholesterol.

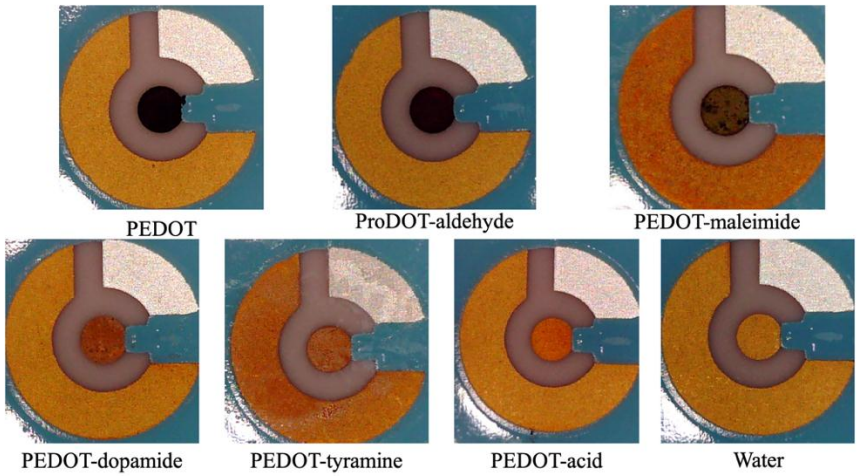


Figure 7: Functional PEDOTs conjugated polymer films deposited on screen printed electrodes using a total charge of 0.15 C/cm^2.

Electrochemical Polymerization

Each of these monomers has shown the ability to be electrochemically deposited onto substrates, although the efficiency of film deposition is clearly a function of chemistry and the composition of the solvent used, as well as the composition of the electrode. We typically use water as the deposition solvent, since it is readily available and is ubiquitous in biological systems. We have found that adding small amounts of propylene carbonate (PPC) to water creates a binary solvent mixture (88 vol% water:12 vol% PPC) that is particularly effective in assisting in polymer film formation. This is

presumably because the PPC helps to solubilize the monomer, yet still allows for precipitation of the polythiophene film as the molecular weight increases.

Figure 7 shows a series of functionalized polythiophenes electrochemically deposited onto a 1.6 mm diameter gold working screen-printed electrode (available from Metrohm DropSens, 223AT) using 0.2 uA/cm^2 of current for 150 seconds, corresponding a charge density of 0.15 C/cm^2. The films all have a dark blue-black color similar to that of unmodified PEDOT. The thickness of the film is a function of the monomer composition, presumably due to the change in solubility of the resulting polymer in solvent mixture as the side group becomes more hydrophilic, and thus there is less driving force for precipitation from solution.

Polymerization potentials varied significantly for different functional monomers, with the three thickest films requiring the lowest potentials. Deposition of electrically active polythiophene films was confirmed through the change in color of the electrode surface as well as systematic changes the frequency dependent impedance spectra (Figure 8). The changes in both impedance magnitude and phase were highly dependent on the functional monomer used, with some functional polymers showing electrical performances similar to regular PEDOT, with others showing more insulating behavior. These new monomers make it possible for us to tune the chemical composition and corresponding properties of the resulting thiophene copolymers for specific applications.

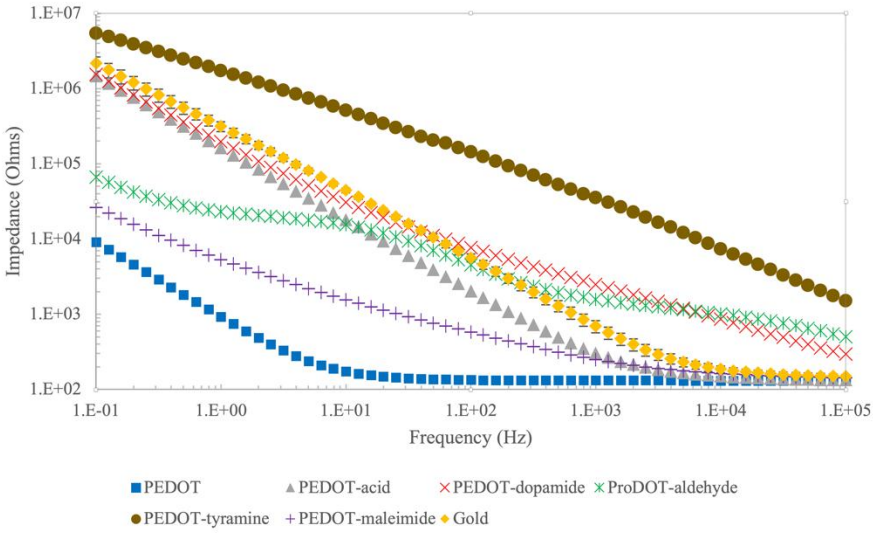


Figure 8: Electrochemical impedance spectra (Bode plot) of various functionalized polythiophenes prepared from the monomers described in this paper.

A thick, dark film of poly(EDOT-maleimide) grown potentiostatically is shown in the optical micrograph of Figure 9. The surface shows a rough surface morphology that correlates with the low impedance seen in the EIS data. These PEDOT-MA films

were found to deposit readily and were highly adherent to the gold electrode. The maleimide functionality is capable of a number of different chemical reactions including Michael addition [15], Diels-Alder reactions [16], cycloaddition [17], free radical polymerization [18], as well as photo- [19] and thermally-induced [20] crosslinking.

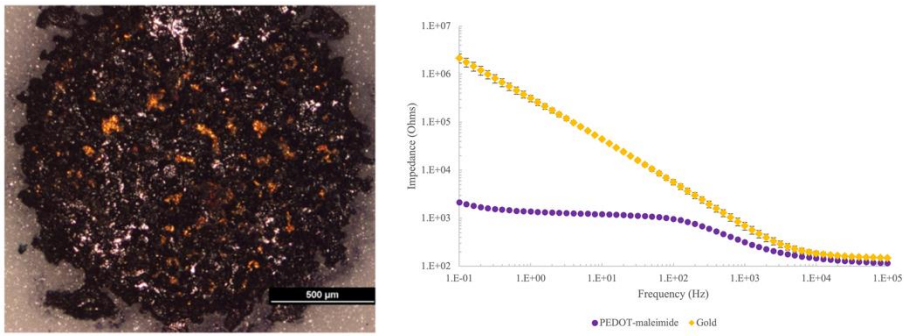


Figure 9. Functional PEDOT-maleimide film. Left: optical micrograph; Right: Bode plot.

Experimental Details:

Materials

Hydroxymethyl EDOT (EDOT-OH), Dess-Martin periodinane, maleic anhydride, glacial acetic acid, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), diisopropylethylamine (DIPEA) 3,4-dihydroxyphenethylamine (dopamine), cholesterol, 4-(dimethylamino)pyridine (DMAP) and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDCI) were purchased from Sigma Aldrich Chemicals, USA and were used as received. EDOT-COOH was purchased from Shanghai Seebio Biotech, Inc. ProDOT-OH [13], EDOT-NH_2 [21–22], EDOT-N_3 [21] and tyramine-maleimide [23] were synthesized according to literature procedures. Sodium thiosulfate, sodium sulfate, sodium hydroxide and hydrochloric acid were procured from Fisher Scientific and were used as received. *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), toluene, chloroform, dichloromethane, ethyl acetate and pet ether were procured from Fisher Scientific.

Measurements

NMR spectra were recorded on a Bruker 400 MHz spectrometer, at resonance frequencies of 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR measurements using $CDCl_3$ and Acetone-d_6 as solvents. Attenuated total reflectance FTIR (ATR-FTIR) spectra of thiophene monomers were recorded on a PerkinElmer Spectrum 100 ATR-FTIR spectrometer. Electrochemical polymerization was carried out using a Metrohm Autolab PGSTAT128N.

Monomer Synthesis

2'-carbaldehyde-3,4-ethylenedioxythiophene (EDOT–aldehyde): Into a 50 mL two necked round-bottom flask fitted with a magnetic stirring bar were added Dess-Martin periodinane (0.443 g, 1.05 mmol) and dry dichloromethane (20 mL). EDOT-OH (0.150 g, 0.871 mmol) was added to the reaction mixture and stirred at room temperature for 12 h, while consumption of starting material was monitored by TLC. After the reaction was complete, 1M sodium thiosulfate (20 mL) was added. After stirring for 15 minutes, the phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The dichloromethane solution was washed with saturated brine solution (2 x 20 mL) and dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using pet ether: ethyl acetate (80:20, v/v) as an eluent to afford EDOT-aldehyde (0.102 g, 69 %). FT-IR: 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.77 (s, 1H), 6.52 (d, 1H), 6.40 (d, 1H), 4.60 (t, 1H), 4.32 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.4, 141.2, 139.9, 100.9, 77.6, 63.7 ppm.

3-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-3-carbaldehyde (ProDOT–aldehyde): Into a 50 mL two necked round-bottom flask fitted with a magnetic stirring bar were added Dess-Martin periodinane (0.508 g, 1.20 mmol) and dry dichloromethane (20 mL). ProDOT-OH (0.200 g, 0.998 mmol) was added in the reaction mixture and stirred at room temperature for 12 h, while consumption of starting material was monitored by TLC. After the reaction was complete, 1M sodium thiosulfate (20 mL) was added. After stirring for 15 minutes, the phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The dichloromethane solution was washed with saturated brine solution (2 x 20 mL) and dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using pet ether: ethyl acetate (80:20, v/v) as an eluent to afford ProDOT-aldehyde (0.154 g, 78 %). FT-IR: 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.80 (s, 1H), 6.51 (s, 2H), 6.40 (d, 1H), 4.47 (d, 2H), 3.92 (d, 2H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.4, 149.1, 106.0, 74.2, 54.1, 15.3 ppm. Melting point (DSC) was 58.4 C.

2'-maleimideomethyl-3,4-ethylenedioxythiophene (EDOT–MA): Into a 50 mL two necked round-bottom flask equipped with a mechanical stirrer, a gas inlet and a reflux condenser were placed EDOT-NH_2 (0.20 g, 1.16 mmol), maleic anhydride (0.138 g, 1.40 mmol) and glacial acetic acid (10 mL). The reaction mixture was stirred at 120 ^{o}C for 12 h. The reaction mixture was cooled to room temperature and glacial acetic acid removed by evaporation under reduced pressure. The crude product was dissolved in ethyl acetate and the solution was washed with water (3 x 20 mL). The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and ethyl acetate was removed by evaporation under reduced pressure. The crude product was purified by column chromatography using pet ether: ethyl acetate (70:30, v/v) as an eluent to afford pure EDOT-MA (0.16 g, 55%). FT-IR: 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.77 (s, 2H), 6.33 (d, 2H), 4.39 (d, 1H), 4.21 (d, 1H), 3.98-3.88 (m, 2H), 3.73 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.2, 141.0, 134.3, 100.2, 70.9, 66.1, 37.7 ppm. Melting point (DSC) was 102.4 C.

N-(3,4-dihydroxyphenethyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-2-carboxamide (EDOT-dopamide): Into a 100 mL two necked round-bottom flask equipped with a

magnetic stirrer and argon gas inlet were placed EDOT-COOH (1.0 g, 5.37 mmol), anhydrous *N, N*-dimethylformamide (50 mL). DIPEA (3.08 mL, 17.72 mmol) and HATU (2.25 g, 5.91 mmol) were added together at room temperature. After 30 minutes dopamine (1.53 g, 8.06 mmol) was added and stirred overnight at room temperature. Afterwards, *N, N*-dimethylformamide was removed under reduced pressure and the crude product dissolved in ethyl acetate (100 mL). The organic phase was washed with water (3 x 100 mL), dried over sodium sulfate and the solvent removed under vacuum. The crude product was purified by column chromatography using pet ether: ethyl acetate (80:20, v/v) as an eluent to afford EDOT-dopamide (0.68 g, 80 %). FT-IR: 3331, 2744, 1664, 1620 cm^{-1}; ^{1}H NMR (400 MHz, Acetone-d_6): δ=7.74 (s, 1H), 6.93 (d, 1H), 6.75 (d, 1H), 6.73 (s, 1H), 6.58 (dd, 1H), 6.44 (d, 1H), 5.42 (d, 1H), 4.53 (d, 1H), 4.06 (dd, 1H), 3.51-3.46 (m, 2H), 2.73 (t, 2H); ^{13}C NMR (100 MHz, Acetone-d_6): δ=162.1, 147.1, 145.9, 144.1, 142.2, 131.9, 120.9, 116.6, 116.1, 110.7, 100.5, 95.4, 60.6, 42.0, 35.8 ppm. Glass transition temperature (DSC) was -10 C.

EDOT-tyramine: Into a 50 mL necked round-bottom flask equipped with a mechanical stirrer, a gas inlet and a reflux condenser were added EDOT-N_3 (0.20 g, 1.01 mmol), tyramine-maleimide (0.241 g, 1.11 mmol) and dry chloroform (10 mL). The reaction mixture was stirred at 60 ^{o}C under nitrogen atmosphere for 12 h. The reaction mixture was cooled to room temperature and chloroform removed by evaporation under reduced pressure. The crude product was dissolved in ethyl acetate and the solution was washed with water (2 x 30 mL). The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and ethyl acetate was removed by evaporation under reduced pressure. The crude product was purified by column chromatography using pet ether: ethyl acetate (80:20, v/v) as an eluent to afford pure EDOT-tyramine (0.308 g, 70%). FT-IR: 3225, 1704, 1614, 1596, 1515 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ=8.21 (s, 1H), 6.48 (d, 2H), 6.72 (dd, 2H), 6.49-6.44 (m, 2H), 5.62 (dd, 1H), 4.64-4.62 (dd, 2H), 4.36-4.29 (m, 1H), 4.12-4.01 (m, 3H), 3.61 (t, 2H), 2.73 (t, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ=173.3, 171.6, 157.0, 142.5, 130.7, 129.3, 116.2, 100.5, 83.6, 73.05, 66.7, 60.5, 49.5, 41.0, 32.9 ppm. Melting point (DSC) was 145.1 C.

EDOT-cholesterol: Into a 100 mL two necked round-bottom flask equipped with a mechanical stirrer and a nitrogen inlet were added EDOT-COOH (0.20 g, 1.07 mmol), cholesterol (0.415 g, 1.07 mmol) and dichloromethane (20 mL). DMAP (0.131 g, 1.07 mmol) was added to the reaction mixture and stirred at ambient temperature. After 10 min, EDCI (0.412 g, 2.14 mmol) was added to the reaction mixture in one portion. The mixture was stirred overnight at room temperature. Then the mixture was extracted with dichloromethane (3 x 30 mL) and washed with brine. The combined organic layers were dried by sodium sulfate and evaporated under vacuum to give crude product, which was purified by silica-gel column chromatography using pet ether: ethyl acetate (95:5, v/v) to obtain the EDOT-cholesterol (0.472 g, 77 %). FT-IR: 1760, 1706 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ=6.48 (d, 1H), 6.36 (dd, 1H), 5.39 (s, 1H), 4.75 (m, 2H), 4.35 (d, 2H), 2.23 (q, 2H), 2.03-1.83 (m, 5H), 1.61-1.25 (m, 13H), 1.17-0.86 (m, 23H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ=167.1, 140.5, 139.0, 123.2, 100.3, 75.9, 72.2, 65.6, 56.5, 49.9, 42.3, 39.5, 37.8, 36.8, 36.5, 36.1, 35.8, 31.8, 28.2, 28.0, 27.6, 24.2, 23.8, 22.8, 22.5, 21.0, 19.3, 18.7, 11.8 ppm. Melting point (DSC) was 161.1 C.

Electrochemical deposition: Polymerization of EDOT and functional EDOTs and ProDOTs was done in a cosolvent mixture of 88% water: 12% propylene carbonate by volume with lithium perchlorate counter ion using galvanostatic methods. Functional EDOT and ProDOT concentrations were all 0.01 M, counter ion at 0.02 M, and a control solution was composed of DI water. For a polymerization a 50 μL drop of monomer solution was dropped onto the electrode surface, completely covering the three electrodes. A charge density of 1.5 mC/mm^2 was used for polymerization with a current of 10 μA/mm^2 for 150 seconds on Dropsens commercially available screen printed electrodes 223AT. The electrodes used were composed of a 1.6 mm diameter gold working electrode, gold counter electrode and silver pseudo reference electrode.

Acknowledgements

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