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Thiophene-Based Trimers for In-Vivo Electronic Functionalization of Tissues

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ABSTRACT: Electronic materials that can self-organize in-vivo and form functional components along the tissue of interest can result in seamless integration of the bioelectronic interface. Previously we presented in-vivo polymerization of the conjugated oligomer ETE-S in plants, forming conductors along the plant structure. The EDOT-thiophene-EDOT trimer with a sulfonate side group polymerized due to the native enzymatic activity of the plant and integrated within the plant cell wall. Here we present the synthesis of three different conjugated trimers based on thiophene and EDOT or purely EDOT trimers that are able to polymerize enzymatically in physiological pH in-vitro as well as in-vivo along the roots of living plants. We show that by modulating the backbone and the side chain we can tune the electronic properties of the resulting polymers as well as their localization and penetration within the root. Our work paves the way for rational design of electronic materials that can self-organize in vivo for spatially-controlled electronic functionalization of living tissue.

KEYWORDS: EDOT, conducting polymers, enzymatic polymerization, plant mediated polymerization, bioelectronics, tissue engineering

1. Introduction

The interplay between electronic and ionic conduction in conjugated polymers makes them efficient transducers in bioelectronic devices where ionic signals are translated in electronic readout and vice versa.¹⁻³ In addition, the soft nature of conjugated polymers renders them compatible with the biological milieu and stable within it.⁴ Thiophene and its derivatives, especially 3,4-ethylenedioxythiophene (EDOT) have been widely explored in organic bioelectronics, while the commercially available poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) has been the benchmark material in many devices such as neural probes,^{5,6} biosensors,^{7,8} and electronic scaffolds for cell culture.⁹ While traditionally the bioelectronic interface is being built independently of the tissue, recent work highlights the possibility of developing the interface directly on the tissue with examples reported both in animals, for modulating neural activity, and in plants, for energy applications. Martin and coworkers were the first to demonstrate this concept by electropolymerization of EDOT directly in the brain of a mouse.^{10,11} Recently Bao and coworkers took another approach where they genetically modified neuronal cells in order to express enzymes that then polymerized aniline dimers directly onto the cell surface.¹² Whereas in animals, so far, either physical or chemical trigger is required for the polymerization of the conductor, we

have shown that in plants the native physicochemical environment is sufficient to self-organize poly(4-(2,3-dihydrothieno[3,4-b]-[1,4]dioxin-2-yl-methoxy)-1-butananesulfonic acid, sodium salt) (PEDOT-S)¹³ and to polymerize the bis[3,4-ethylene dioxothiophene]-3-thiophene butyric acid, sodium salt, trimer (ETE-S),¹⁴ forming conductors integrated into the plant structure. By investigating the mechanism, we revealed that the presence of the peroxidase enzymes in the plant and the native concentration of hydrogen peroxide were sufficient for the enzymatic polymerization of the ETE-S trimer and for the integration of the polymer into the plant cell wall.¹⁵ Enzymatic polymerization of conjugated polymers has been demonstrated in in-vitro conditions primarily at low pH for aniline,^{16,17} as well as for EDOT.^{18,19} So far, the ETE-S trimer is the only example of enzymatically polymerized conjugated molecule in physiological pH. Importantly, ETE-S being a water-soluble thiophene-based trimer, allows the preparation of stable and ready-to-use solutions, and suites better biological applications than aniline and its derivatives. Moreover, the trimeric structure of ETE-S is advantageous since it comprises a middle thiophene group that can be used as an anchor site for further functionalization, while the two external EDOT molecules have lower oxidation potential with respect to EDOT or thiophene monomers, rendering the trimer very reactive and facilitating its polymerization. These already set the basis of design principles that should be followed for the

synthesis of new conjugated molecules that are able to polymerize in-vivo in order to build bioelectronic interfaces directly on tissue. Following these principles, we present herein the synthesis of three new water-soluble thiophene-based trimers and we demonstrate their ability to polymerize in-vitro and in-vivo within living plant tissue via enzymatic polymerization. Starting from ETE-S, we propose a new, more efficient route for its synthesis and we prepare an ETE trimer functionalized with a cationic ammonium derivative. Cationic PEDOT has been recently proposed by Mecerreyes and coworkers as a new, water-soluble, cathode material that exploits the cation to inhibit electrostatic repulsion with anions present in aqueous media.²⁰ Given the complex biological environment where in-vivo polymerization takes place, functionalizing ETE with a cation would give an extra handle for engineering its interactions with the surrounding medium. In this case ETE doping would not be self-induced but rather indirect, induced by the anions that stabilize the cation and/or negative charges that are present in the biological medium. Therefore, we expect that the presence of the cationic moiety will impact doping strength, resulting in a conducting material with a lower oxidation level than ETE-S, which still retains water solubility. Besides ETE-based trimers, we synthesize novel trimers by attaching three EDOT monomers in a row, denoted hereafter EEE. Mimicking ETE-S and ETE-cation, two EEE trimers were prepared, one functionalized with an anionic sulfonate group at the side chain and another bearing a trimethylammonium cation. EEE trimers are expected to exhibit a lower oxidation potential than their ETE counterparts and, thus, polymerize easier. Moreover, by replacing the middle thiophene with EDOT conductivity is expected to increase.

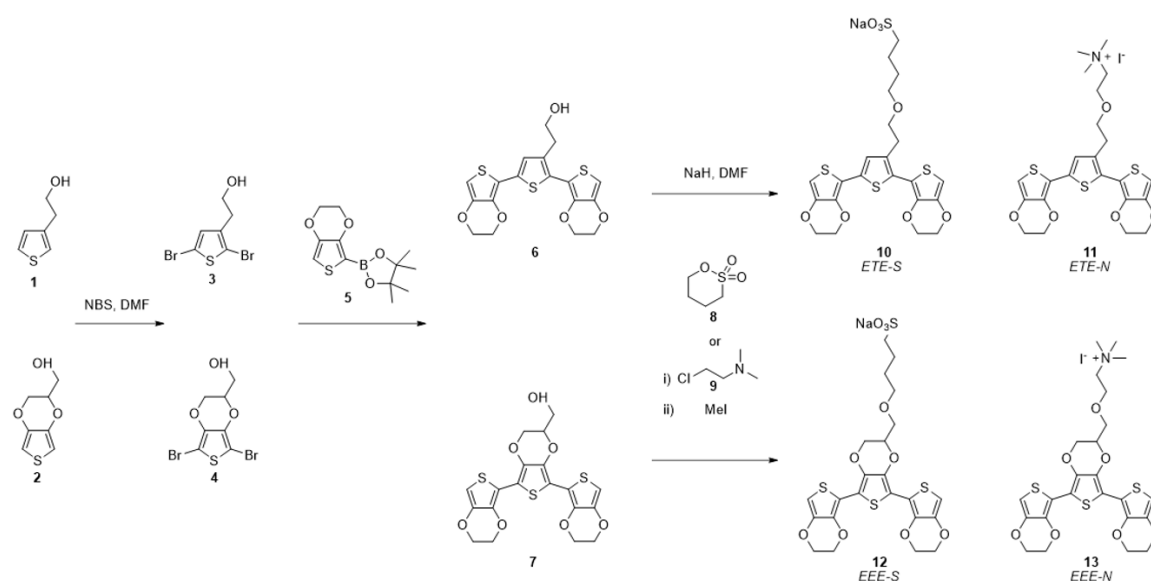
2. Result and Discussion

The synthesis of trimers 10-13 (Scheme 1) was achieved following a customizable route that involves few synthetic steps

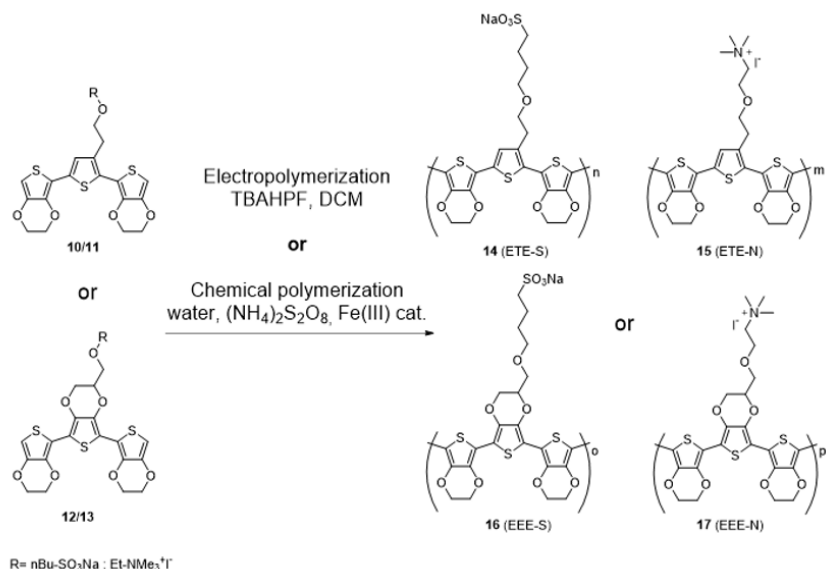
and results in improved yields with respect to synthetic routes previously reported for EDOT-based molecules.¹⁴ As far as ETE-S (10, Scheme 1) is concerned, it has been previously synthesized applying 4 synthetic steps: di-bromuration of the thiophene scaffold, propane sultone addition and Suzuki reaction with a mono boronic acid EDOT derivative (Supporting Information, Scheme S7).¹⁴

This strategy is specific to ETE-S and the as-prepared trimer is not suitable for further modifications, since the linkable hydroxy group has been converted into the sulfonate derivative during the first step. However, if the hydroxyl function of the thiophene ring is kept active, and a trimer-OH molecule is obtained, this trimer can be easily functionalized in a later step.²¹ This strategy is extremely beneficial, since further chemical modification can be performed directly on the trimer rather than on the initial monomer, thus reducing the synthetic steps needed for the generation of trimers with different functional groups. Starting from 3-(2-hydroxyethyl)thiophene (1), the hydroxyl-functionalized ETE trimer is obtained (6). Starting from hydroxymethyl EDOT (2) and its dibrominated derivative (4), we prepared the all-EDOT alter ego of ETE-OH, i.e. EEE-OH (7).

Next, two synthetic routes were pursued in order to introduce negative or positive charges on Trimers 6 and 7 through the hydroxyl groups. By reaction with butane sultone, 6 and 7 were converted to their negatively charged sulfonate forms 10 (ETE-S) and 12 (EEE-S) in acceptable yields. In order to obtain their positively charged counterparts, 6 and 7 were mixed with 2-chloro-N,N-dimethylethylamine for the introduction of a tertiary amine, as described in literature for EDOT derivatives.²⁰ Next, an excess of iodomethane was used to convert



Scheme 1. Scheme of synthetic pathways of Trimers 10-13.



Scheme 2. Scheme of synthetic pathways of polymerization of the four trimers, resulting in polymers 14-17.

the amine into its stable quaternized salt, resulting in the two cationic derivatives **11** (ETE-N) and **13** (EEE-N). The structure of trimers **10-13** was confirmed by proton and carbon-13 nuclear magnetic resonance (¹H/¹³C-NMR) spectroscopies, heteronuclear single quantum correlation (HSQC) 2D-NMR spectroscopy and ATR FT-IR spectroscopy. The data are pre-

sented in Supporting Information, Sections 2.4 - 2.7. Additionally, it is highlighted that all synthetic steps can be easily performed by non-synthesis specialists, since the synthetic pathway mostly consists of operations of precipitation and filtration and only one column chromatography (after the Suzuki coupling reaction) is required.

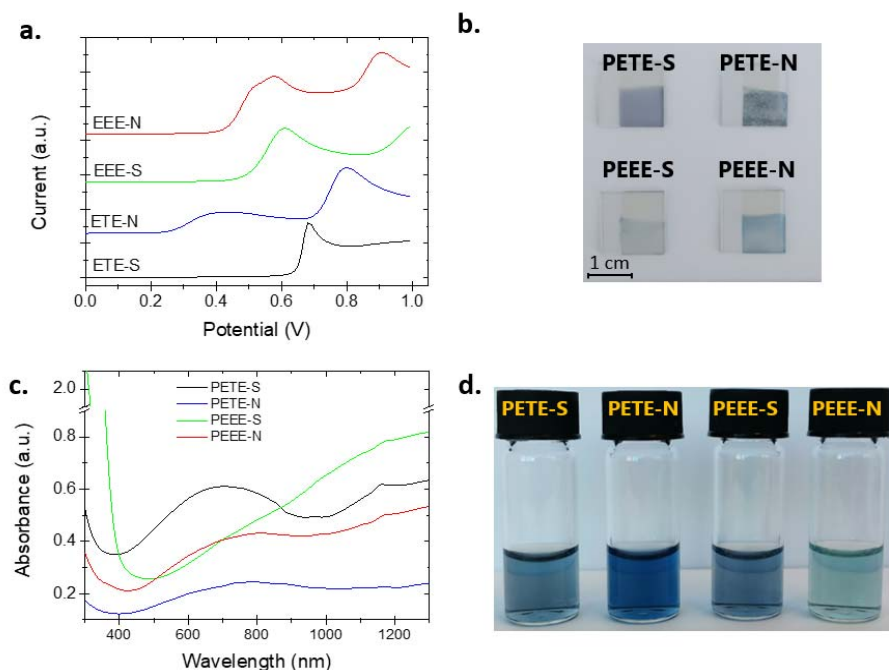


Figure 1. (a) Cyclic voltammetry curves recorded during the anodic scan of the 1st electropolymerization cycle of the four trimers. Curves are presented shifted along the Current axis for clarity. Electropolymerizations were performed with 1mM solution in acetonitrile, using 0.1M of TBAHFP as the electrolyte. (b) Electropolymerized PETE-S, PETE-N, PEEE-S and PEEE-N films, supported on

ITO/glass. (c) UV-vis-NIR absorption spectra of the chemically polymerized aqueous dispersions of PETE-S, PETE-N, PEEE-S and PEEE-N. (d) the corresponding dispersions.

The route described herein is highly reproducible, and it is believed to be a suitable and friendly tool for interdisciplinary researchers. Following synthesis, the four polymers were electrochemically, chemically and enzymatically polymerized in-vitro. Polymerization in living plant roots was induced via the native enzymes of the plants (Scheme 2). Electrochemical polymerizations to obtain polymers **14-17** (denoted hereafter as PETE-S, PETE-N, PEEE-S and PEEE-N) were carried out using 0.1 M of Tetrabutylammonium hexafluorophosphate (TBAHFP) as electrolyte in 1 mM acetonitrile solution of the different trimers **10-13**. In order to evaluate the potential electrodeposition of these molecules, cyclic voltammetry was performed on precoated indium tin oxide (ITO) glass substrates. During electropolymerization, an anodic potential in the range of 0 – 1 V was applied, and oxidation led to the growth of polymer films on ITO for all four trimers. The successful electrodepositions of the four monomers were confirmed by the constant increase of current between consecutive cycles (Figure S16) and they were completed after 10 cycles. Thin polymeric films were finally formed for all materials.

Figure 1a presents the anodic part of the 1st electropolymerization cycle of the four trimers. The two sulfonate-bearing trimers exhibit a single oxidation peak in the range 0 – 1 V, related to the oxidation of the external EDOT units of the trimers where chain elongation occurs. The oxidation peak recorded for EEE-S is located in a lower potential range with respect to ETE-S. The oxidation onset of EEE-S is at 0.47 V while that of ETE-S is at 0.63 V, indicating that EEE-S polymerizes easier than ETE-S, as expected. ETE-N has two oxidation peaks, a very broad one located at low potentials (onset at 0.25 V) which we attribute to the electrical compensation of the ammonium cations that energetically should arrive before the oxidation of the trimer's ends, and a sharper peak at 0.8 V (onset at 0.7 V) that we attribute to the oxidation of ETE-N that drives its polymerization. Comparing the oxidation (polymerization) onsets of ETE-N and ETE-S we conclude that the cationic moiety shifts the polymerization of ETE towards higher potentials. Concerning EEE-N, its voltammogram includes a double peak around 0.5 V and a single peak at 0.9 V. Following the same reasoning as for ETE-N, the oxidation of EEE-N towards PEEE-N should be represented by the high potential peak. These multiple peaks are in agreement with previously reported literature on polythiophene derivatives and indicate that introduction of chemical functional groups can lead to additional oxidation reactions.²²⁻²⁴ Note that the oxidation potential of bare EDOT is 1.4 V,²⁵ much higher than the potentials recorded for the four trimers, which is justified by the larger extension of conjugation in the case of trimers.

Figure 1b presents representative photos of the electrodeposited films which appear blue on ITO. The surface morphology was imaged by means of Atomic Force Microscopy

(AFM) (Supporting Information, Figure S19). The surface of the PETE-S, PEEE-S and PEEE-N films appears quite homogeneous and with a low roughness, while PETE-N exhibits large protrusions.

The oxidative polymerization of the four trimers to derive polymers **14-17** was performed using ammonium persulfate as the oxidant and iron (III) as the catalyst. The polymerization was carried out for 18 h at room temperature. Dark blue/green dispersions were obtained and subsequently characterized by UV-vis-NIR and ATR FT-IR spectroscopies. Derivatives **10-13** are fully water-soluble and, thus, it was not necessary to use PSS or other stabilizers that are commonly used in the polymerization of EDOT. Herein, the anionic moieties on ETE-S and EEE-S effectively behave as the sulfonate groups of PSS, inducing self-doping. The positively charged groups on ETE-N and EEE-N are expected to act as cationic surfactants. Such cationic surfactants have already been successfully used to stabilize and dope PEDOT.^{20,26,27}

The UV-vis-NIR absorption spectra of all polymeric dispersions are presented in Figure 1c, while photos of the dispersions are presented in Figure 1d. The successful polymerization is confirmed by the absence of the neat trimers absorption peaks between 300 and 400 nm (*cf.* Figure 2a). The appearance of broad absorption bands above 500 nm is consistent with the formation of conjugated polythiophene backbones. Specifically, for PEEE-S and PEEE-N, the broad vis-NIR absorption is assigned to both polaronic and bipolaronic states in the band gap, following the recent DFT-based interpretation reported by Zozoulenko *et al.*²⁸ The more pronounced NIR absorption recorded for PEEE-S implies that this polymer exhibits a higher oxidation level than PEEE-N, corroborating the more efficient doping induced by the anion, in accordance with our initial hypothesis on the role of the cation. Concerning PETE-S and PETE-N, the broad absorption peaks centered at 700 and 780 nm, respectively, are indicative of the polymers doping with bipolaron charge carriers.²⁹ Once more, the higher absorption recorded for PETE-S above 1000 nm is consistent with a higher oxidation level of the anion-bearing polymer. For all four polymers, no peaks related to neutral chains are observed at around 550 nm,^{28,29} underlining the efficient doping of the polymers.

The conductivity of these new polymers in thin film configuration was measured using the four-point probe technique. The conductivities of PEEE-S and PEEE-N are 170 and 2 S cm⁻¹, much higher than those of PETE-S and PETE-N (25 and 0.5 S cm⁻¹), validating the hypothesis behind the design of EEE trimers which suggests that all-EDOT trimers will conduct charges better than ETE trimers³⁰ due to enhanced planarity. Moreover, the sulfonate-bearing trimers are more conducting than their cationic counterparts, in consistence with their higher doping level. Note that the conductivities measured for

the four trimers are higher than the 0.2 - 0.35 S cm⁻¹ values reported for PEDOT:PSS thin films without any additives,³¹⁻³³ partially due to the absence of the electronically insulating PSS counterpart, but also due to the self-induced doping in the case of the anionic-bearing trimers, or due to the indirect (medium-induced) doping, in the case of the cationic-bearing trimers.

Next, the in-vitro enzymatic polymerization of the four trimers was evaluated. We have previously reported that the

ETE-S trimer polymerizes efficiently in the presence of horse radish peroxidase (HRP) and hydrogen peroxide in physiological pH.¹⁵ Here, the successful enzymatic polymerization of ETE-S synthesized following the novel synthetic route is achieved, as expected. The UV-vis spectrum of the reaction solution (ETE-S 360 μM, H₂O₂ 180 μM, HRP 5 U mL⁻¹) recorded after 5 min of incubation shows that the trimer ETE-S peak diminishes and a broad absorption band appears from 500

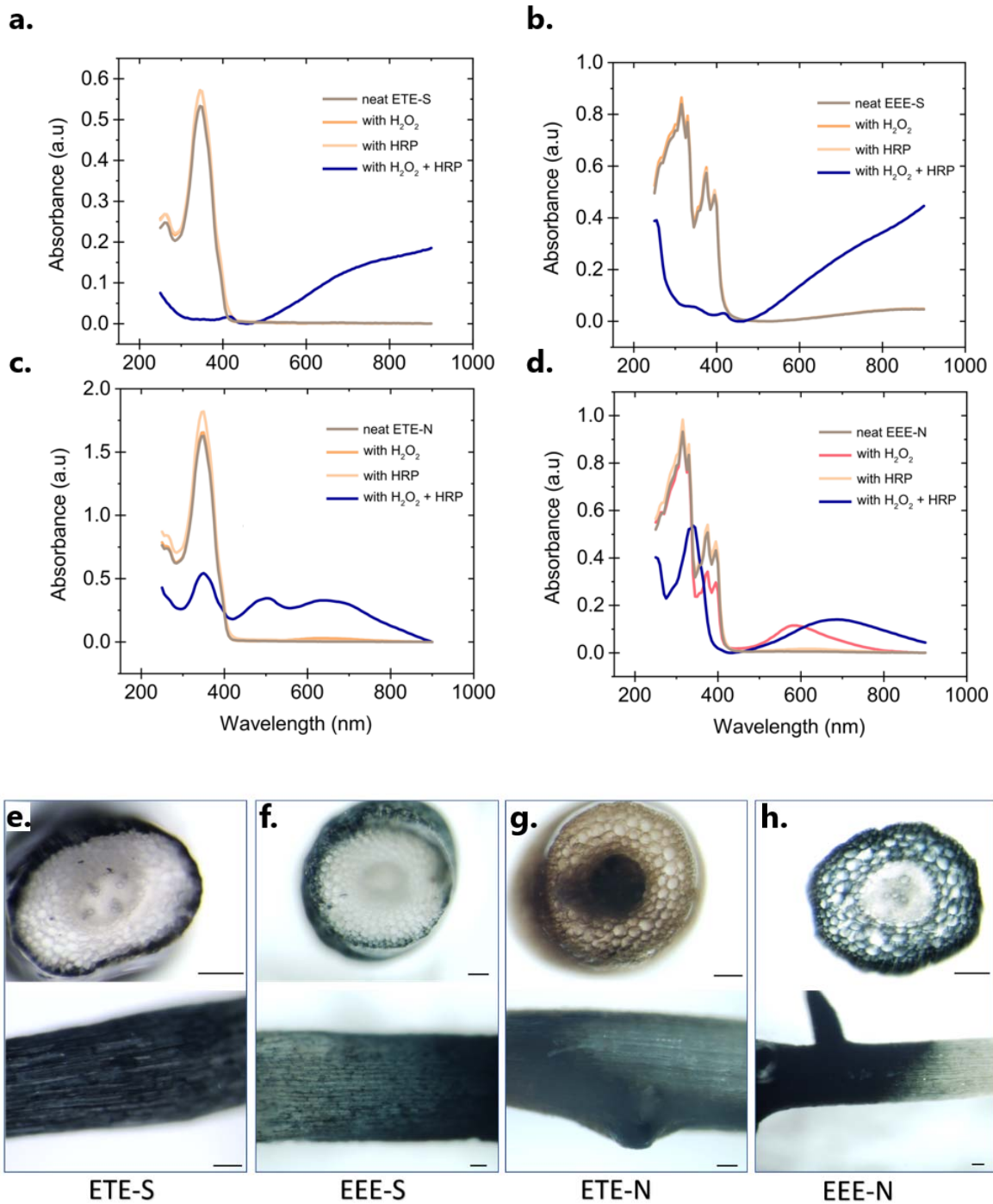


Figure 2. Enzymatic in-vitro polymerization of (a) ETE-S, (b) EEE-S, (c) ETE-N and (d) EEE-N. UV-vis spectra of neat trimer in DI water (360 μM), trimer (360 μM) in presence of hydrogen peroxide (180 μM), trimer (360 μM) in presence of HRP (5 U mL⁻¹) and trimer (360 μM) in presence of both hydrogen peroxide (180 μM) and HRP (5 U mL⁻¹) after 5 minutes of reaction. (e)-(h) Cross-sections (top) and lateral views (bottom) of bean roots in-vivo functionalized for 24 hours with 1 mM mL⁻¹ of e) ETE-S, f) EEE-S, g) ETE-N and h) EEE-N. The scale bar is 100 μm.

nm to NIR (Figure 2a), which corresponds to the doped state of PETE-S.²⁹ When HRP or H₂O₂ are not included in the reaction solution, no polymerization occurs, as shown by the absorption signature of ETE-S at 350 nm that remains unaltered. Similar behavior was recorded for EEE-S (Figure 2b) which polymerizes only when both HRP and H₂O₂ are present in the reaction solution. The high absorption of the formed PEEE-S at NIR is assigned to polaronic and bipolaronic bands, as it was previously described for PEDOT,^{13,34} and confirms the efficient self-doping of this polymer.

Concerning enzymatic polymerization of the two cation-bearing trimers, the absorption spectra exhibit new peaks in the visible range that prove that polymerization does occur upon addition of H₂O₂ and HRP. Nonetheless, the presence of the neat trimers signature at around 350 nm demonstrates that polymerization is not complete after 5 min of reaction, as not all trimers are consumed, and suggests that ETE-N and EEE-N are less reactive than ETE-S and EEE-S. This is probably driven by the lower solubility of these molecules in water, which can affect polymerization kinetics, slowing down the polymerization rate. Furthermore, this could arrive by a higher charge stabilization provided by the sulfonate group during polymerization.

Since absorption properties are highly defined by the backbone due to its high electron density, we move on and assign the ETE-N peaks based on the DFT calculations for ETE-S.²⁹ The absorption peak at 500 nm matches very well the absorption from neutral (undoped) PETE chains, while that at 650 nm can be attributed to polaronic states of single oxidized oligomers or to bipolaronic states formed in π - π PETE stacks. Note that this later peak is blue-shifted with respect to the one predicted for PETE-S. We attribute this shift to the presence of the positive charge on the side chain since counterions are expected to affect the band position in the gap due to Coulomb interactions,²⁸ besides, of course, the strong effect of oligomer length and chain packing on absorption. In contrast, Figure 2d shows that EEE-N already polymerizes in the presence of H₂O₂, thanks to the presence of OH radicals. However, the formed polymer is in the reduced (neutral) state. When HRP is added in the reaction, a broad band centered at 700 nm appears, related to the doped state of the polymer. Similarly to ETE-N, this peak is blue-shifted with respect to the polaronic/bipolaronic peak predicted for PEDOT at 800 nm.²⁸ No NIR absorption is recorded. Therefore, enzymatically polymerized PETE-N and PEEE-N are found to be only partially doped after 5 mins of reaction, and to exhibit a low oxidation level. Certainly, this is a result of the positively charged side chain that inhibits charge depletion from the backbone, favoring the undoped state. As already mentioned above, any charges in the backbone are then stabilized by anions present in the reaction solution. These findings highlight the efficient use of the side chain charge as a handle for tuning oxidation level, and, subsequently, conduction properties.

After the successful in-vitro enzymatic polymerization of the four trimers, we proceed to evaluate their in-vivo polymerization, using bean roots as the model system. A

fresh root from a bean plant was immersed in a 1 mM trimer solution for 24 hours. Then the root was detached from the plant and observed under a stereomicroscope. In all cases, the trimers polymerize along the root, localized on the epidermis, forming a dark blue coating, in agreement with the in-vitro experiments. Just like PETE-S, PEEE-S localizes on the epidermis without penetrating within the internal structure of the root (Figure 2e and 2f). In the case of EEE-N and ETE-N polymerization is observed not only on the epidermis of the root but also within the ground and vascular tissue. EEE-N polymerizes around the cell wall of the cortex cells as seen from the cross-section (Figure 2h) while ETE-N crosses the pericycle and enters within the vascular tissue (Figure 2g). The reason for the ability of these trimers to pass the epidermis and enter internally should be related to the functionalization of the conjugated backbones with a positively charged side chain. The in-vitro experiments showed that the positively charged moieties slow down the polymerization process. Possibly, these slow kinetics allow the smaller and more mobile trimers to penetrate easier the plant's tissue before polymerizing. Moreover, the reduced water solubility of the cation-bearing trimers compared to the anion-bearing ones may drive the penetration of the former molecules deeper inside the root, where environment is less aqueous. This hypothesis could be supported by the fact that ETE-N is less soluble than EEE-N and, thus, manages to reach the innermost of the root, and enters the vascular tissue.

In all cases the trimers polymerize only on the part of the root that has been immersed in the trimer solution. Even in the cases where the trimers enter the internal structure of the root, no trimer is found in the part of the root that was not immersed in the solution, indicating, thus, that these trimers travel only laterally within the root and not longitudinally.

3. Conclusion

In conclusion, the synthesis of three new EDOT-based trimers that can be used as conducting building blocks in bioelectronics has been presented. The trimers can be chemically, electrochemically and enzymatic polymerized in vitro. Functionalizing the side groups with anions or cations proves to be an efficient way to tailor the doping level, as well as the oxidation potential, which consequently affects the polymerization kinetics. Furthermore, the trimers can be efficiently polymerized in-vivo along the roots of living plants due to the presence of native peroxidase enzymes. The localization of the resulting polymer in the roots depends on the trimer structure. This work not only offers to bioelectronics community a set of new water-soluble EDOT-based materials for tissue interface, but, most importantly, draws design principles for the synthesis of self-organized conducting molecules for electronic functionalization of living tissue.

4. Experimental Section

Synthesis of the four trimers (10,11,12,13 in Figure 1a). The synthesis was performed using butane sultone and N,N-di-

methylamino-2-chloroethane together with sodium hydride in anhydrous DMF. Then, iodomethane was used to quaternize the amine, obtaining the ammonium derivative. In all cases, the product is an insoluble powder and has been recovered by filtration. All details are provided in Supporting Information, Section 2. Details on polymerizations (chemical, electrochemical, in-vitro and in-vivo) as well as on characterization methods are provided in Supporting Information.

ASSOCIATED CONTENT

Supporting Information. Materials and Methods, Synthesis & NMRs (Dibromuration of 1 and 2; Synthesis of EDOT boronic acid pinacol ester 5; Suzuki Coupling Reactions (Trimer-OHs) (6,7); ETE-S (10); EEE-S (11); ETE-N (12); EEE-N (13)); Previous synthesis of ETE-S by Stavrinidou et Al.; Cyclic voltammetry; ATR FT-IR of chemically polymerized 14-17; Films preparation and conductivity values; AFM measurements. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

Any additional relevant notes should be placed here.

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