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Rapid Voltammetric Measurements at Conducting Polymer Microelectrodes Using Ultralow-Capacitance Poly(3,4-ethylenedioxythiophene):Tosylate

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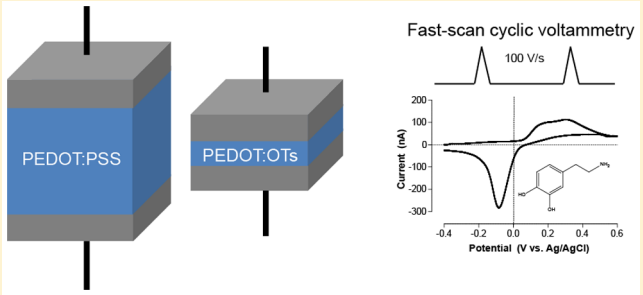
ABSTRACT: We use a vapor-phase synthesis to generate conducting polymer films with low apparent capacitance and high conductance enabling rapid electrochemical measurements. Specifically, oxidative chemical vapor deposition was used to create thin films of poly(3,4-ethylenedioxythiophene):tosylate (PEDOT:tosylate). These films had a conductance of 17.1 ± 1.7 S/cm. Furthermore, they had an apparent capacitance of 197 ± 14 μF/cm^2, which is an order of magnitude lower than current commercially available and previously reported PEDOT. Using a multistage photolithography process, these films were patterned into PEDOT:tosylate microelectrodes and were used to perform fast-scan cyclic voltammetry (FSCV) measurements. Using a scan rate of 100 V/s, we measured ferrocene carboxylic acid and dopamine by FSCV. In contrast to carbon-fiber microelectrodes, the reduction peak showed higher sensitivity when compared to the oxidation peak. The adsorption characteristics of dopamine at the polymer electrode were fit to a Langmuir isotherm. The low apparent capacitance and the microlithographic processes for electrode design make PEDOT:tosylate an attractive material for future applications as an implantable biosensor for FSCV measurements. Additionally, the integration of PEDOT:tosylate electrodes on plastic substrates enables new electrochemical measurements at this polymer using FSCV.



INTRODUCTION

As the need for new analytical tools grows greater, conducting polymers are emerging as attractive materials for electrochemical and biological applications.[1−3] Compared to traditional electrode materials such as carbon or noble metals, conducting polymers are low-cost and quickly synthesized, processed, and patterned into a variety of geometries.[4−6] Furthermore, PEDOT-based electrode coatings are commonly used to extend the lifetime of implantable probes for electrochemical and electrophysiological measurements in the brain.[7,8] When used as an electrode material, PEDOT has been shown to have good electron-transfer kinetics for biogenic amines (e.g., dopamine, serotonin, and norepinephrine).[1,9] Furthermore, it exhibits the ability to electrochemically resolve dopamine and ascorbic acid[10] or as a coating to resolve catecholamines and serotonin over ascorbic acid and uric acid in the presence of SDS.[11] PEDOT has also been used to measure neurotransmitter release from living systems.[1,12] The surface properties of this material make PEDOT an ideal candidate for an electrode material to make other types of measurements in the brain such as using fast-scan cyclic voltammetry (FSCV) to detect neurotransmitters. FSCV is used to measure the release of biogenic amine neurotransmitters in the brain, typically using carbon-fiber microelectrodes (CFMEs).[13,14] However, CFMEs are limited to disk or cylindrical geometries. Besides the characteristics listed above, using PEDOT as the electrode material will enable novel or nontraditional electrode substrates and geometries to target specific brain regions or create arrays that could be used to record from multiple sites.

PEDOT is an attractive material for a wide variety of applications outside of neurochemistry because of its relatively high and uniform sheet conductance and high specific capacitance while also having unique properties as a material such as being lightweight, optically transparent, and flexible.[15−21] Substantial effort has been devoted to further increasing the conductivity of PEDOT films through doping, covalent modification, or chemical treatments. These efforts have succeeded in increasing the conductivity of PEDOT:PSS from 1 S/cm (as a commercially available preparation) to values on the order of 1000−3000 S/m.[16−23] However, when using PEDOT as an electrode material for chemical measurements, including FSCV, the capacitance must be minimized. When making rapid electrochemical measurements, the

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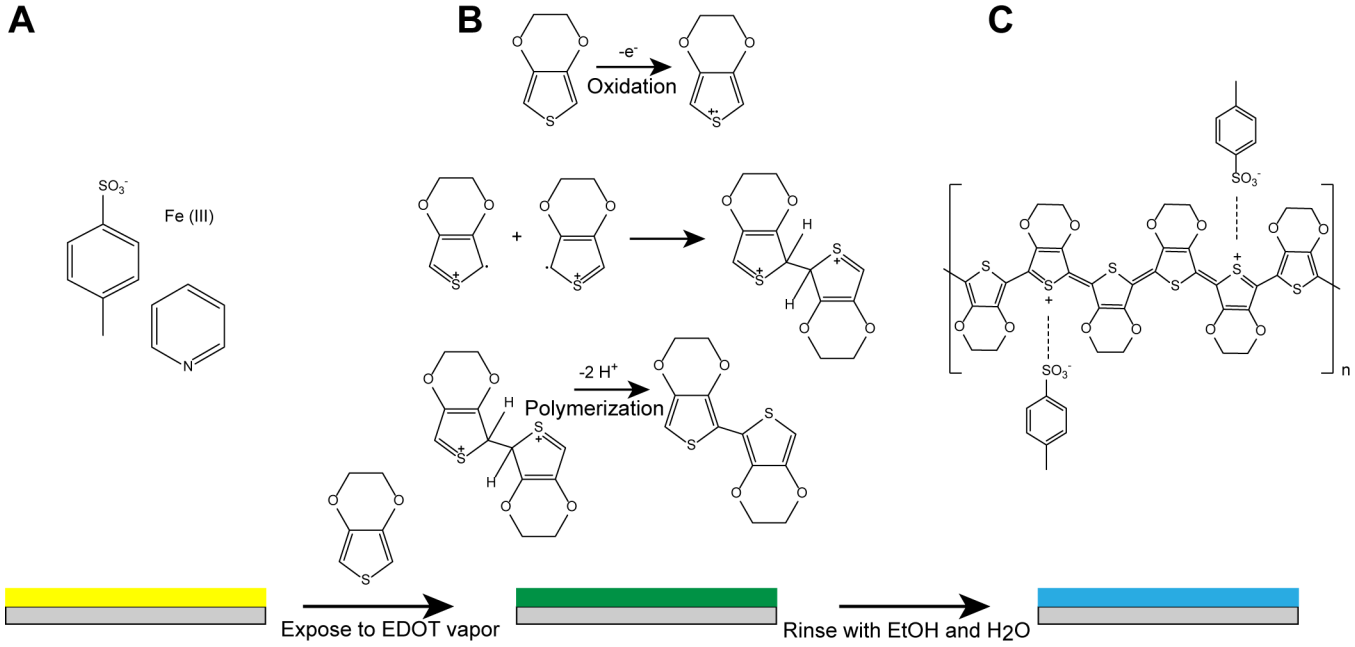
Scheme 1. Synthesis Method Used to Create PEDOT:Tosylate Films[a]



[a](A) A solution of iron(III) tosylate and pyridine in *n*-butanol is deposited on a substrate surface. (B) The substrate is exposed to EDOT monomer vapor at 55 °C for 20 min to allow polymerization to occur. (C) The substrate is removed from the vapor and rinsed with ethanol and deionized water to remove iron and any remaining reactants. This yields a thin, conductive film of PEDOT:tosylate.

capacitance of the material limits the RC time constant of the electrode, thus limiting the response time.[24] Historically, PEDOT films typically have a high apparent capacitance (~2000 μF/cm^2).[1,25,26] This trend seems to persist even in the presence of different dopants or chemical treatments. To perform electrochemical measurements at high scan rates (>100 V/s), the apparent capacitance of PEDOT needs to be lowered to a value closer to that of traditional electrode materials, such as CFMEs (~100 μF/cm^2).[27]

Herein we introduce a synthesis based on vapor-phase deposition to create PEDOT:tosylate films.[28−33] We have optimized this method to lower the apparent capacitance of PEDOT:tosylate by an order of magnitude compared to commercially available PEDOT:PSS and previously reported PEDOT:tosylate (197 ± 14 vs 2390 ± 130 or 1670 ± 130 μF/cm^2, respectively).[1] This reduction in capacitance, coupled with low resistance, allows for a scan rate of 100 V/s to be used to perform electrochemical measurements by FSCV. This, combined with a multilayer photolithography technique to pattern PEDOT:tosylate microelectrodes,[5,34] has allowed us to perform the first FSCV measurements at a polymer electrode. Additionally, the adsorption characteristics and quantitative response for dopamine were measured. We demonstrate the potential utility of low-capacitance PEDOT:tosylate for rapid measurements of neurotransmitters. This will enable researchers to explore this new material to access novel electrode geometries and microelectrode arrays to study the brain with FSCV, which is not currently possible with CFMEs that possess low capacitance but are limited geometrically. Additionally, lowering the capacitance of PEDOT for uses outside of solution-phase electrochemistry gives rise to new options for many solid-state devices that include a PEDOT layer. Applications that would benefit from lower capacitance PEDOT materials such as solar cells, flexible electronics, and coatings for implantable sensors are long-term targets for this improved material.[3,17,35]

EXPERIMENTAL SECTION

Chemicals. Unless noted, all chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received. Solutions were prepared using 18.2 MΩ·cm water purified using a Milli-Q gradient A-10 system (EMD Millipore, Darmstadt, Germany). TRIS artificial cerebrospinal fluid (aCSF; pH 7.4; 15 mM Tris·HCl, 125 mM NaCl, 2.5 mM KCl, 25 mM $NaHCO_3$, 1.2 mM NaH_2PO_4, 2.0 mM Na_2SO_4, 2.4 mM $CaCl_2$, 1.2 mM $MgCl_2$) was used for all electrochemical measurements. All analyte solutions were prepared in TRIS aCSF immediately before use.

Vapor-Phase PEDOT:Tosylate Film Synthesis. TOPAS 5013L cyclic olefin copolymer (Topas Advanced Polymers Inc., Florence, KY, USA) substrates (Ø 50 mm × 2 mm wafers) were generated via injection molding. PEDOT:tosylate films were deposited by spin coating using a CEE model 100 spin-coating system (Brewer Science, Rolla, MO, USA) with 1 mL of 20% w/v iron(III) tosylate in *n*-butanol and anhydrous pyridine at 1500 rpm for 15 s with an acceleration of 500 rpm/s onto TOPAS substrates (Scheme 1A). The pyridine concentration was varied to control the rate of polymerization and the film thickness. The coated substrates were placed in a glass Petri dish and covered. Ethylenedioxythiophene (EDOT) monomer (~100 μL) was deposited at the bottom of the dish, and the dish was placed on a hot plate with a surface temperature of 55 °C to evaporate the monomer. The dish containing the substrates was removed after 20 min, and the substrates were removed immediately. At this time, the films changed from yellow to blue-green, indicating the successful deposition of the PEDOT film (Scheme 1B). PEDOT:tosylate-coated substrates were rinsed with 18.2 MΩ·cm water to remove residual iron(III) tosylate and then dried using N_2 (Scheme 1C). This rinse step yielded a blue film. Substrates were placed in a 70 °C oven to dry overnight.

PEDOT:PSS Film Synthesis. Glass slides were cleaned with Alconox and ethanol, rinsed with 18.2 MΩ·cm water, and dried under N_2. A thin adhesion layer composed of poly-3,4-ethylenedioxythiophene:polystyrenesulfonate (PEDOT:PSS) was spin-coated onto these

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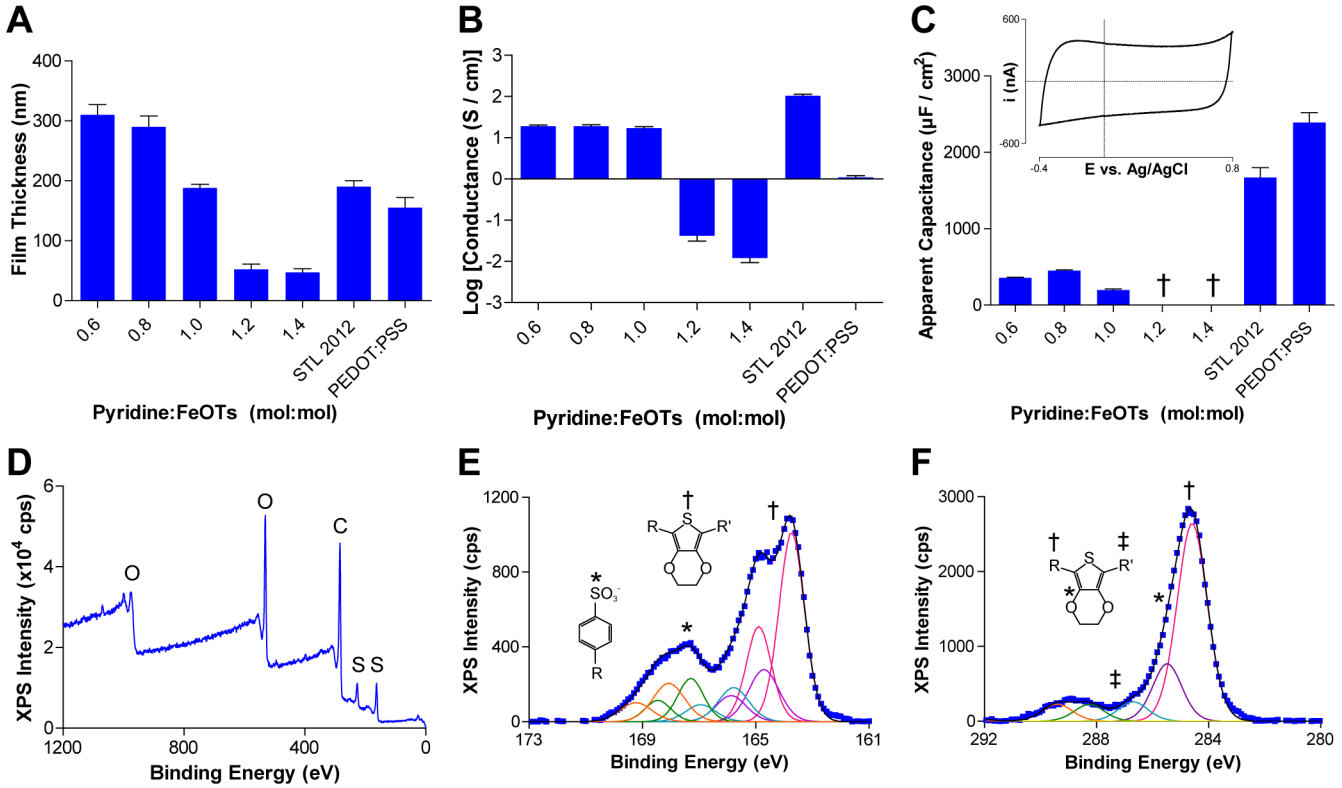

Figure 1. Electrical and chemical properties of PEDOT:tosylate electrodes. (A) Thickness of the PEDOT films as a function of the synthesis conditions/method used, measured by profilometry. (B) Conductance of PEDOT films as a function of the synthesis conditions or method used. The data shows that solutions containing an equimolar or smaller amount of pyridine to iron(III) tosylate generate highly conductive films (>10 S/cm). However, excess pyridine results in a poorly conductive film; these were not further evaluated. (C) The apparent capacitance of PEDOT films as a function of the synthesis conditions or method used, measured using cyclic voltammetry. The apparent capacitance is lower when a vapor-phase synthesis is used, and it is minimized using an equimolar ratio of pyridine to iron(III) tosylate. The inset is a cyclic voltammogram obtained at a 1.0 molar ratio of the PEDOT:tosylate electrode (electrode area, 10^{-2} cm^2; scan rate, 100 mV/s; buffer, TRIS aCSF, pH = 7.4). The daggers (†) represent data points not tested because of low conductance (error represents ±SEM, n = 4–5 electrodes). Solution-phase PEDOT:tosylate values are reported from Larsen et al.[1] (D) Full XPS spectrum of PEDOT:tosylate film. (E) Sulfur 2p region of the XPS spectrum showing peaks for both PEDOT at 164–165 eV and the tosylate dopant at 168 eV.[19] Using the ratio of these peaks, we can determine the doping ratio of the film. (F) Carbon 1s region of the spectrum showing a large peak at 285 eV with smaller peaks at 286 and 288 eV.[19] The large peak corresponds to a high fraction of alkyl carbon that exists only in the region where the monomers polymerize whereas the other peaks correspond to C–O and C═O, which are not very abundant. This suggests that this material has very long polymerized chains with minimal insertions of oxygen-containing groups that would occur at the site of chain terminations.

substrates at 5000 rpm for 60 s at an acceleration of 5000 rpm/s and baked on a hot plate at 200 °C for 10 min. This baking step yielded a nonconducting adhesion layer (<30 nm thickness). An additional layer of high-conductivity-grade PEDOT:PSS (3% w/w in water) was spin-coated onto the substrate at 3000 rpm for 30 s with an acceleration of 3000 rpm/s and dried at 70 °C in an oven overnight.

Electrode Patterning and Fabrication. PEDOT:tosylate electrodes were patterned using UV lithography as previously described by Vreeland et al.[4] In brief, the AZ3312 photoresist (AZ Electronic Materials, Branchburg, NJ, USA) was spin coated using a WS-650-23 spin coater (Laurell Technologies Corp., North Wales, PA, USA) on the PEDOT:tosylate-coated substrates at 3000 rpm for 10 s at an acceleration of 1000 rpm/s. The substrates were then soft baked on a hot plate at 100 °C for 2 min before a 15 s contact exposure (9.0 mW cm^{-2}, 365 nm) on a Karl Suss MJB3 mask aligner (SÜSS MicroTec AG, Garching, Germany) through a positive-tone printed plastic photomask (CAD/Art Services, Inc.) containing several electrodes. Substrates were then baked on a hot plate at 100 °C for 2 min and cooled on a benchtop before two sequential 30 s submersions in AZ351 MIF developer with agitation. The substrates were then rinsed twice with 18.2 MΩ·cm water and dried using N_2. A microwave-generated plasma etching process[4] (two to three cycles, 10 s each) was used to remove unprotected features yielding well-defined electrodes. After etching, substrates were rinsed with semiconductor-grade acetone to remove the photoresist and rinsed with ethanol and then water prior to use. Photolithography for PEDOT:PSS films was performed in the same manner as for the PEDOT:tosylate electrodes.

X-ray Photoelectron Spectroscopy. All X-ray photoelectron spectra were acquired with a KratosAxis Ultra 165 DLD spectrometer equipped with a magnetic immersion electron lens using 300 W monochromatic Al Kα radiation in constant analyzer energy mode. The sample analysis area used was 700 μm × 300 μm. Survey spectra were collected using a pass energy of 160 eV, and specific elemental regions were collected using a 20 eV pass energy and averaged over multiple scans. The analysis chamber was maintained at a pressure of $\leq 5 \times 10^{-9}$ Torr.

PEDOT:Tosylate Microelectrode Chip Fabrication. For FSCV measurements, PEDOT:tosylate microelectrodes were fabricated with gold electrical contacts to minimize the effect of sheet resistance (leading to an ohmic loss in the film) on electrochemical measurements (Figure 2). The electrodes and the contacts were embedded into TOPAS 5013L polymer substrates using the method described by Matteucci et al.[5] The only modifications made to the process were the use of thicker TOPAS 5013L substrates (2 mm thickness), and PEDOT:tosylate deposition was performed using the vapor-phase method (vide supra). After fabrication, electrodes were insulated with an acrylic polymer leaving only the PEDOT and the contact pads exposed (Figure 2D).

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Conductance Measurements and Surface Characterization. Conductivity was measured with a four-point probe (Jandel Engineering, Bedford, U.K.) connected to a Keithley 2400 SourceMeter (Keithley Instruments, Cleveland, OH, USA) using currents in the 1−10 μA range. The thickness of the PEDOT films was measured using an Alpha-Step AS-200 profilometer (KLA-Tencor, Milpitas, CA, USA). Optical micrographs were collected using a Nikon Ti-2000 microscope (Nikon Corporation, Tokyo, Japan).

Electrochemistry. Electrochemical data was collected using an Ensman EI-400 potentiostat (Ensman Instruments, Bloomington, IN, USA) and custom LabVIEW software (National Instruments, Austin, TX, USA). Electrical contact to the electrode was established using a graphite conductive adhesive (Alfa Aesar, Ward Hill, MA, USA) and silver wire painted onto the contact pad. For cyclic voltammetry experiments, the electrode geometry was defined by placing a 6-mm-diameter PDMS well on top of the electrode and filling it with TRIS buffer solution. The reference (Ag/AgCl QRE) and counter (Ag) electrodes were submerged in this well to create an electrochemical cell. Slow-scan cyclic voltammograms were collected at 10−100 mV/s and swept from −0.4 V to 0.6−0.8 V vs a Ag/AgCl quasi-reference electrode. All slow-scan data were hardware low-pass filtered at 40 Hz. Apparent capacitance values were calculated using eq 1 (Figure 1C). To determine if the microelectrode chip geometry and high scan rates had an effect on the apparent capacitance, background scans with the microelectrode chip were collected at scan rates ranging from 1 to 100 V/s, and the data were treated in the same manner (eq 1, Figure 3B,C).

The microelectrode chip was also tested by measuring ferrocene carboxylic acid, a well-characterized redox-active probe molecule. Measuring at a scan rate of 100 mV/s, a quasi-steady-state cyclic voltammogram was collected (Figure 3A). Theoretical quasi-steady-state band electrode currents were calculated using eq 2 and compared to the experimentally measured value.[36]

FSCV. Fast-scan cyclic voltammetry measurements were collected using hardware and software provided by Knowmad Technologies (Tucson, AZ, USA). Software was written in LabVIEW 2013 (National Instruments, Austin, TX, USA). The waveform was generated and the data were acquired using a PCIe-6363 DAC/ADC card (National Instruments, Austin, TX, USA). Current was measured using a CHEM-CLAMP voltammeter (Dagan Corporation, Minneapolis, MN, USA). All data was hardware low-pass filtered at 10 kHz and software filtered using a fourth-order low-pass Butterworth filter (f_c = 1.00 kHz) and zero phase filtered.[37] Electrochemical cells were prepared on PEDOT:tosylate microelectrode chips by placing a 6 mm PDMS well on top of the electrode and filling it with TRIS buffer solution. The electrode length was defined by the application of the insulating acrylic layer described above. The reference electrode (Ag/AgCl QRE) was submerged in this well to create an electrochemical cell. Fast-scan cyclic voltammograms were collected by applying a triangle waveform swept from −0.4 to 0.6 V vs Ag/AgCl QRE at a scan rate of 100 V/s. This waveform was applied at frequency of 1.0 Hz. All electrodes were cycled for 20 min in buffer before measurements were made.

Cyclic voltammograms were obtained by collecting backgrounds for 10 s, flooding the cell with the analyte of interest for 10 s and then rinsing with a constant stream of buffer for 10 s for a total collection time of 30 s. Between experiments, the cell was rinsed with five volumes of fresh buffer to remove any residual analyte, and a 30 s background was collected. Using this method, solutions containing ferrocene carboxylic acid and dopamine were measured.

RESULTS AND DISCUSSION

PEDOT Film Properties. PEDOT electrodes must have high conductivity and low apparent capacitance to perform rapid electrochemical measurements. Commercially available[23] and previously synthesized[1] PEDOT have the requisite conductivity, but they possess high capacitance (~2000 μF/cm^2), which limits their utility. Thus, we developed and characterized a vapor-phase synthesis to minimize the capacitance of PEDOT films. PEDOT:PSS films are made by spin coating commonly used commercially available solutions, whereas here PEDOT:tosylate films are made using vapor-phase deposition. To make PEDOT:PSS films, glass substrates were used as a result of a more-uniform coating generated from aqueous solutions. For the PEDOT:tosylate films, TOPAS 5013L was used as the substrate because it is compatible with the organic solvents used in the vapor-deposition process. It is important to note that effective and even wetting of the surface dictate the quality of the film. During the vapor-phase PEDOT:tosylate film synthesis, several ratios of the starting materials, pyridine and iron(III) tosylate, were tested (Scheme 1A) to optimize the film for both high conductivity and low apparent capacitance. The different synthesis conditions included molar ratios with less pyridine than iron(III) tosylate (0.6:1.0 and 0.8:1.0 mol/mol), excess pyridine (1.2:1.0 and 1.4:1.0 mol/mol), and an equimolar ratio (1.0:1.0 mol/mol). All five ratios resulted in the formation of blue films. Pyridine has been shown previously to drastically affect the rate of the polymerization when added in small amounts.[38,39] We optimized the amount of this reactant, using relatively high loadings compared to those in previous works, to achieve slow growth. Furthermore, we used a reaction temperature (55 °C vs 70+ °C) and oxidant loading (20% w/v compared to 40%) that are on the lower end of the range of previously reported values with the goal of creating long, conjugated polymer structures with fewer chain breaks and interfaces in order to minimize the capacitance.[38,40,41]

We investigated if our synthesis method resulted in films of differing thicknesses. Using profilometry, we determined that too little pyridine results in thick films (ca. 300 nm), whereas too much pyridine results in very thin films (ca. 50 nm). The equimolar ratio yielded films with a similar thickness to what we have previously reported for a solution-phase synthesis (188 ± 6 nm compared to 190 ± 10^1 nm, ±SEM, n = 5, Figure 1A). The PEDOT:PSS spin-coating method yielded films with a thickness (155 ± 17 nm) comparable to our equimolar-ratio vapor-deposited films.

Before they were used as electrodes, the surface resistivity of these films was measured to determine their conductance. Using a four-point probe to measure the surface resistivity combined with the thickness of the films, a bulk conductance of the material was calculated (Figure 1B).[42] Vapor-phase-synthesized films prepared using 0.6:1.0, 0.8:1.0, and 1.0:1.0 molar ratios resulted in PEDOT:tosylate films with conductance values greater than 10 S/cm. However, excess pyridine, in ratios of 1.2:1.0 or 1.4:1.0, yielded very resistive films with conductance values on the order of 10^{-2} S/cm. From this, we concluded that exceeding an equimolar ratio of pyridine to oxidant retards polymerization too much and should not be considered further because of their high resistivity. For reference, untreated commercially available high-conductivity PEDOT:PSS was measured to have a conductance of 1.1 ± 0.1 S/cm (±SEM, n = 5), in agreement with previously reported literature.[23] Our previously reported solution-phase-synthesized PEDOT:tosylate has a conductance of 103 ± 13 S/cm.[1] Because a low conductance of the electrode material would increase the total resistance of an electrochemical system, only films which had conductance values greater than that of PEDOT:PSS were used as electrodes.

Electrochemical Characterization. Once the films were patterned and etched into electrodes, their electrochemical properties were probed using cyclic voltammetry. First, the

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apparent capacitance was determined by measuring the nonfaradaic current measured in artificial cerebrospinal fluid (aCSF) at a scan rate of 100 mV/s (Figure 1C). Then, the apparent capacitance (C_{app}) was calculated by

$$C_{app} = \frac{i_{1/2}}{A\upsilon} \quad (1)$$

where $i_{1/2}$ is the half-wave current (measured at +50 mV in a flat region), A is the electrode area, and υ is the scan rate. For the electrodes used here, $A = 1.5 \times 10^{-2}$ cm^2 and $\upsilon = 0.1$ V/s. In all cases, the vapor-phase-synthesized PEDOT:tosylate has a much lower apparent capacitance than the PEDOT:PSS or solution-phase PEDOT:tosylate (Figure 1C).[1] The equimolar ratio of pyridine to iron(III) tosylate resulted in the lowest overall apparent capacitance, 197 ± 14 μF/cm^2 (±SEM, $n = 5$). This value is significantly lower than for solution-phase PEDOT:tosylate (Student's t test, $p < 0.0001$) or commercially available PEDOT:PSS (Student's t test, $p < 0.0001$). Moving forward, the synthesis conditions using an equimolar ratio of pyridine to iron tosylate were chosen for all future experiments. The results of all measurements described above are shown in Table 1. Our synthesis conditions (Scheme 1), specifically, tuning the ratio of pyridine to iron tosylate, greatly reduce the apparent capacitance of PEDOT:tosylate electrodes while simultaneously maintaining a high conductance. These two features make this material capable of scan rates required for fast-scan cyclic voltammetry measurements, but the large electrode area (10^{-2} cm^2) limits the scan rates that can be used.

Table 1. Material and Electrochemical Properties of PEDOT Electrodes

material	thickness (nm)	conductance (S/cm)	apparent capacitance (μF/cm^2)
PEDOT:tosylate (0.6:1.0 mol ratio)	310 ± 17	19.2 ± 1.3	357 ± 10
PEDOT:tosylate (0.8:1.0 mol ratio)	290 ± 18	19.2 ± 1.7	450 ± 10
PEDOT:tosylate (1.0:1.0 mol ratio)	188 ± 6	17.1 ± 1.7	197 ± 14
PEDOT:tosylate (1.2:1.0 mol ratio)	52 ± 9	0.042 ± 0.012	N/A
PEDOT:tosylate (1.4:1.0 mol ratio)	47 ± 6	0.013 ± 0.003	N/A
PEDOT:tosylate (STL et al. 2012)[1]	190 ± 10	104 ± 6	1670 ± 130
PEDOT:PSS	155 ± 17	1.05 ± 0.07	2390 ± 130

XPS Analysis. To determine the chemical characteristics of these films that give rise to the low capacitance, we used X-ray photoelectron spectroscopy (XPS). The XPS spectra showed several features characteristic of PEDOT films with the primary signals arising from C 1s, O 1s, S 2s, and S 2p regions because these are the primary components of both the polymer and the dopant (Figure 1D). With regard to the unique chemical makeup of these films, the most interesting regions are the C 1s and S 2p. First, by examining the S 2p region, we find that there are three predominant features (Figure 1E). The two features at lower binding energy (164–165 eV) are from sulfur on the PEDOT chains where the feature at the higher binding energy (~168.5 eV) is from the sulfonate on the tosylate dopant. The PEDOT peaks are much larger than the tosylate peak, indicating that our synthesis method results in a very PEDOT-rich film compared to previous reports.[19,21,43−45] Furthermore, we can use the ratio of these peaks to determine a relative dopant concentration in the film of 1 dopant molecule per 2.9 monomer units. This is reflected in the structure included in Scheme 1. This alone does not explain the low capacitance of the material, but having a high density of conductive chains should create fewer interfaces at which charge can accumulate. However, the most interesting feature with respect to the chemical nature of the low capacitance in these films is in the C 1s region. In this region, there are again three primary features that we examined. The largest peak at 285 eV is from carbon that has only carbon−carbon bonds. When examining the structure of PEDOT, these bonds are created during polymerization as monomer units are joined. The other two features, at 286 and 288 eV, are from carbon−oxygen bonds, with the lower binding energy being from a single bond and the higher binding energy resulting from a double bond.[19,28] The feature at 286 eV would arise from the carbons bound to the oxygens on the ethylenedioxy backbone of the molecule, but the source of the highest-binding-energy feature is not readily apparent from the structure shown here. That is because one of the most abundant polymer end groups for PEDOT is a ketone. Because we have a very small signal in this region, we can determine that we have few polymer end groups, which indicates that we have a very long average chain length. This structural evidence allows us to understand why, when using what are nominally the same polymer and dopant, we can achieve a low apparent capacitance.

PEDOT:Tosylate Microelectrode Chip Validation. To perform fast-scan measurements using PEDOT:tosylate, microelectrodes with small electroactive areas (<10^{-4} cm^2) were patterned. If the electrode area is large, then the nonfaradaic current generated would be too large for most potentiostats to effectively measure. Furthermore, we wanted to minimize resistive losses caused by using PEDOT as the primary conductive material for long (>1 cm) stretches on the chip. To do this, we used a photolithography process whereby gold electrical contacts were patterned onto a substrate followed by the vapor-phase deposition of PEDOT:tosylate (Figure 2A,C). Microelectrodes were fabricated such that a small portion of the PEDOT overlapped with the gold to create an electrical contact, but the majority of the PEDOT was in direct contact with the substrate. An insulating layer was then deposited such that only the PEDOT was exposed to solution (Figure 2B,D).

To test that the exposed PEDOT was both conductive and electroactive, a well-characterized molecule, ferrocene carboxylic acid, was analyzed with slow-scan cyclic voltammetry. A quasi-steady-state cyclic voltammogram was obtained (Figure 3A) that agrees well with the theoretical quasi-steady-state current (i_{qss}). At a thin band electrode, this is described by the equation

$$i_{qss} = \frac{2\pi FlDC}{\ln\left[\frac{64Dt}{w^2}\right]} \quad (2)$$

where C is the bulk concentration of the analyte, D is the diffusion coefficient, F is Faraday's constant, t is the approximate time at steady state, and w (width) and l (length) are the dimensions of the electrode.[24] Using the difference in current before the oxidation peak and the current 100 mV past the half-wave potential, quasi-steady-state current values were measured. These were compared to theoretical values calculated using eq 1 where $D = 4.3 \times 10^{-6}$ cm^2 s^{-1},[46] $l = 1.4 \times 10^{-2}$ cm, $w = 5 \times 10^{-4}$ cm, $n = 1$, $F = 96\,485$ C mol^{-1},

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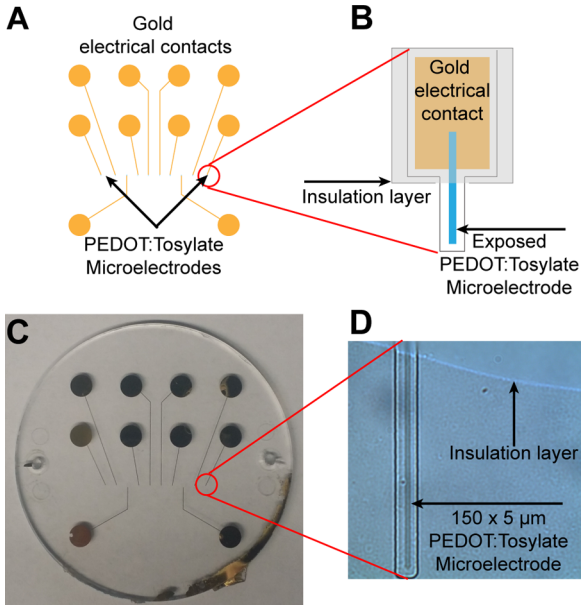

Figure 2. PEDOT:tosylate microelectrode chip used for fast-scan cyclic voltammetry measurements. (A) Drawing of the chip used to generate photolithography masks. (B) Close-up image of the PEDOT:tosylate electrode showing the overlap with gold to create an electrical contact and the insulation layer used to isolate a small electroactive area (~7 × 10^{-6} cm^2). (C) Optical image of the completed chip and (D) optical microscope image of a 150 × 5 μm PEDOT:tosylate microelectrode including the insulation layer.

and t = 1.0 s.[36] This measurement was performed for every electrode immediately before use, and in all cases, the measured value was within 10% of the calculated theoretical value. This indicates that the PEDOT:tosylate microelectrode has an electroactive area congruent with the geometric area.

Higher scan rates were interrogated to determine if the low apparent capacitance observed with the PEDOT films was maintained at high scan rates with a smaller electroactive area. To test this, the nonfaradaic current was measured at scan rates ranging from 1 to 100 V/s (Figure 3B). The average apparent capacitance with this new geometry and high scan rates is 197 ± 7 $\mu F/cm^2$ (±SEM, n = 5 electrodes), which is not statistically different from that of the PEDOT:tosylate electrodes described earlier (Student's t test, p > 0.98, Figure 1B). Furthermore, it was found that the apparent capacitance is not statistically different across a range of high scan rates (Figure 3C, one-way ANOVA, $F_{(6, 7)}$ = 0.0444, p > 0.999). This indicates that these microelectrodes are capable of making rapid electrochemical measurements via FSCV.

FSCV Measurements. The PEDOT:tosylate microelectrode chip was used to make FSCV measurements of two analytes, ferrocene carboxylic acid and dopamine. In these experiments, a triangle waveform was applied from −0.4 to 0.6 V vs Ag/AgCl QRE at a scan rate of 100 V/s. The anodic scan limit was determined by increasing the switching potential by 100 mV and measuring the change in background current over a period of 20 min. The highest limit that was able to achieve a stable background during that time was 0.6 V. After 20 min of waveform application at 1 Hz, there was minimal observable drift, and the average noise of the electrodes was 0.15 ± 0.05 nA (averaged across 10 scans, 1.0 kHz bandwidth, ±SEM, n = 9 electrodes). During this time, the background drifted to a steady level; the majority of this drift was during the first 5 min of cycling, and the largest feature of the drift occurs at the reversal potential. The overall shape of the background remained the same during this entire time (i.e., the resistance and apparent capacitance did not change).

FSCV measurements were made by injecting a bolus of the target analyte into the electrochemical cell followed by rinsing with several volumes of buffer to remove the electroactive species. Ferrocene carboxylic acid was measured using this method (Figure 4A,B). The background-subtracted cyclic voltammogram showed clear oxidation and reduction features with $E_{1/2}$ = 354 ± 19 mV and ΔE_p = 280 ± 26 mV (±SEM, n = 5, Figure 4A). These values are comparable to those published for measurements of ferrocene carboxylic acid (E_0 = 364 ± 19 vs Ag/AgCl) and a scan rate of 100 V/s using CFMEs.[47] The data collected over a 30 s period are shown in Figure 4B using a color plot. A color plot can be used to visualize changes in the entire voltammogram over time by plotting time (x axis) and voltage applied (y axis) as the independent variables and then showing current in false color as the dependent variable. For ferrocene carboxylic acid, the color plot very clearly shows an increase in current at 450−500 mV (the oxidation potential) after 10 s. This decays back to baseline after the analyte is removed at 20 s. A more simple way to show the change in current at the peak oxidation potential is showing a current vs time trace (top of Figure 4B) whereby the current at one

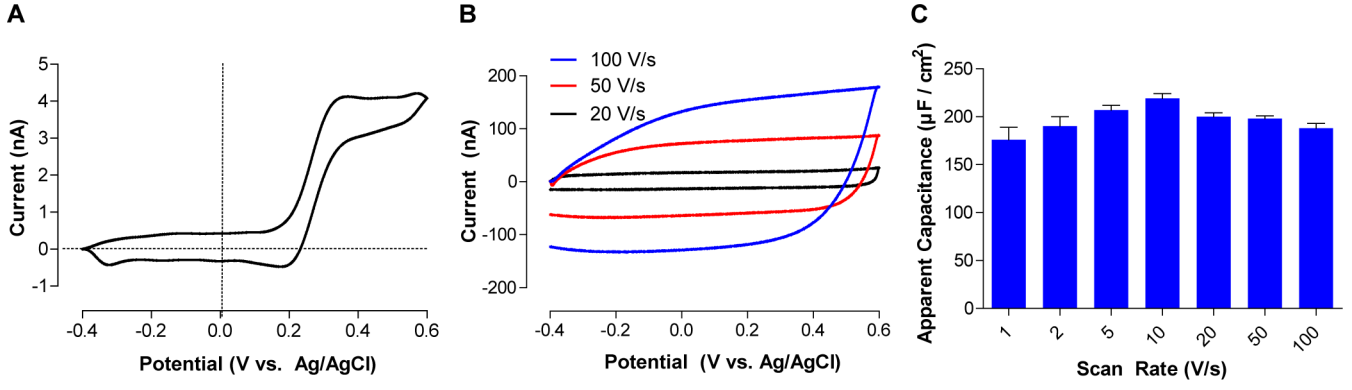

Figure 3. Electrochemical properties of PEDOT:tosylate microelectrodes. (A) Steady-state cyclic voltammogram of 1.0 mM ferrocene carboxylic acid at 100 mV/s used to measure the electroactive area of the PEDOT:tosylate microelectrodes. (B) Nonfaradaic background current measured at PEDOT:tosylate microelectrodes as the scan rate is varied (20 V/s = black, 50 V/s = red, and 100 V/s = blue). (C) Calculated apparent capacitance of the material as a function of scan rate (±SEM, n = 3 electrodes).

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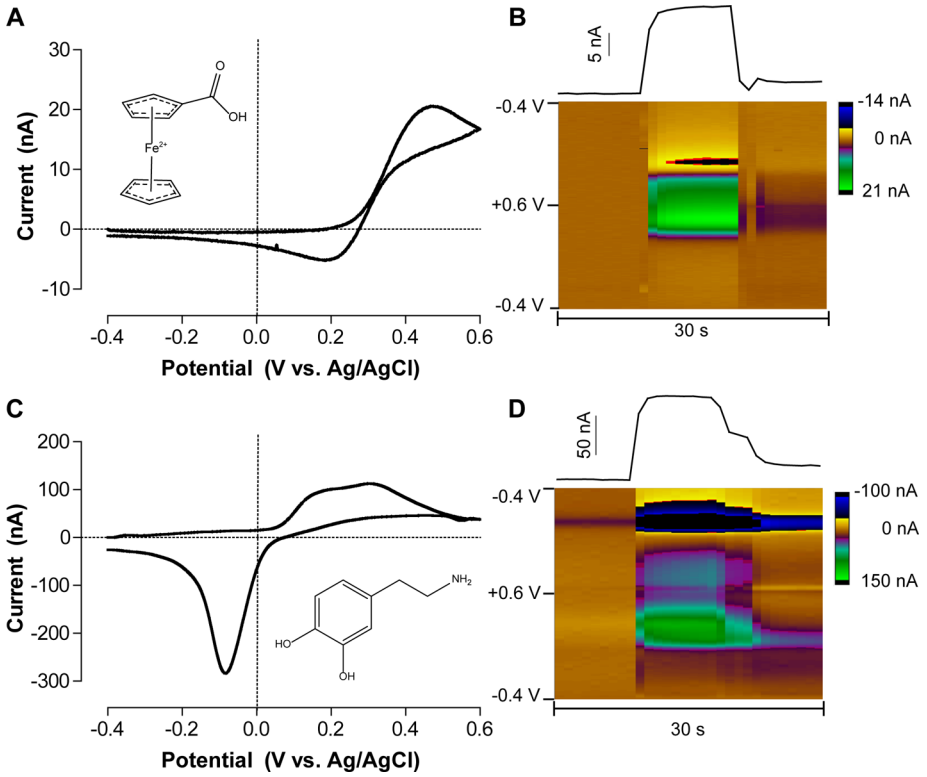

Figure 4. Fast-scan cyclic voltammograms collected at PEDOT:tosylate microelectrodes. (A) Background-subtracted cyclic voltammogram of 10 μM ferrocene carboxylic acid at 100 V/s and (B) color plot and current vs time trace taken at the peak oxidation potential (471 mV). (C) Background-subtracted cyclic voltammogram of 100 μM dopamine at 100 V/s and (D) color plot and current vs time trace taken at the peak oxidation potential (282 mV).

potential is plotted against time. (Think of this as a horizontal slice of a color plot.) The voltammogram, color plot, and current vs time trace all clearly show that PEDOT:tosylate is capable of making rapid voltammetric measurements. After the measurements, the electrodes were again noise tested and found to have an average noise of 0.16 ± 0.05 nA (±SEM, n = 5 electrodes), which is not statistically different than before the measurements (Student's t test, $p > 0.95$).

We wanted to investigate if these electrodes would be a potential candidate platform for FSCV of biogenic amine neurotransmitters. Voltammetry has been used to study neurotransmitter dynamics in the brain for decades because it is rapid and has high sensitivity.[14,48−50] Dopamine was chosen as a model analyte for these measurements because it is both biologically important and has well-characterized electrochemistry.[27,51] The background-subtracted cyclic voltammogram (Figure 4C) contains clear oxidation and reduction features. The anodic scan shows a wide feature that is made up of two peaks, one at 150−200 mV and a second at 350−400 mV. We hypothesize that this could arise from dopamine in two distinct chemical environments: one at the surface of the electrode and the second intercalated into the polymer. Interestingly, the reduction feature is substantially larger in peak amplitude; however, the total charge passed during the oxidation is still greater than that of the reduction (peak area, 260 ± 40 pC vs 220 ± 30 pC, 100 μM dopamine, ±SEM, n = 4 electrodes, paired t test, $p < 0.05$). This could be due to either adsorption of the quinone or intercalation of the analyte into the polymer electrode. Unlike the ferrocene measurements, the color plot does not show a complete decay of the signal upon rinsing with buffer. The persistence of the dopamine signal after rinsing supports the conclusion that dopamine is either adsorbed or intercalated into the polymer. However, the signal returned to background levels after rinsing with 5 buffer volumes, which took approximately 30 s. Furthermore, after measurements the noise of the electrode was found to be 0.54 ± 0.11 nA (±SEM, n = 4), a nearly 4-fold increase compared to before the measurements. Clearly, the presence of dopamine changes the surface of the electrode. The response of the electrode is stable for a time period of 30 to 60 min. The criterion we used to define this is that the size of the background current at +100 mV was at least 80% of that value at t = 0. After that time period, the size of the background and the magnitude of the quantitative signal both decrease, which indicates a loss of electroactive area. Still, the quantitation of dopamine by FSCV is possible. Using the oxidation peak current results in a sensitivity of 1.4 ± 0.3 nA/μM with a limit of detection (LOD) of 0.9 ± 0.3 μM (±SEM, n = 3−4, Figure 5A). Quantitation using the sharper reduction peak gives a greater sensitivity of 3.7 ± 0.8 nA/μM and a better LOD of 0.44 ± 0.13 μM (±SEM, n = 3−4, Figure 5B). Future studies would aim to investigate the selectivity of this reduction in the presence of other redox-active molecules to determine if it could be used for in vivo quantitation. Additionally, work needs to be done to improve device fabrication and electrode insulation to lower the noise to a value under 0.1 nA, the lifetime of the sensor would need to be extended to a period of at least 4−6 h, and the temporal resolution may need to be improved to a value closer to CFMEs that typically operate at 10 Hz. These improvements and optimizations are necessary before this material can be used as an implantable sensor platform for in vivo voltammetry.[50]

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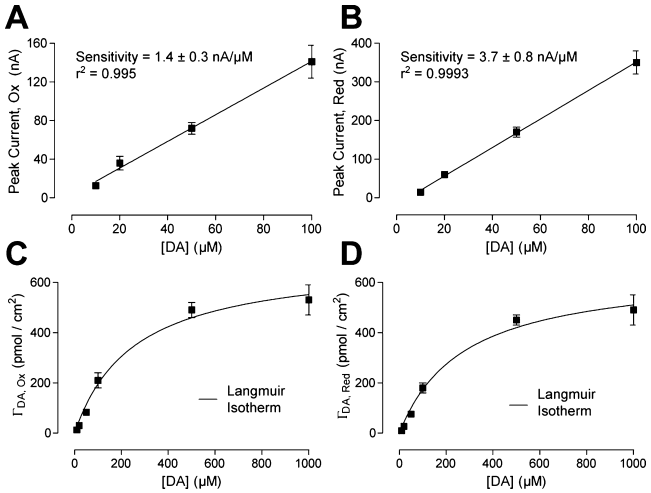

Figure 5. Calibration curves and Langmuir adsorption isotherms for dopamine measured at PEDOT:tosylate microelectrodes by FSCV. (A) Calibration curve generated using the oxidation peak current (±SEM, n = 3–4 electrodes). (B) Calibration curve generated using the reduction peak current (±SEM, n = 3–4 electrodes). (C) Surface coverage of dopamine measured using the integral of the oxidation peak. Data are fit to a Langmuir adsorption isotherm. (D) Surface coverage of dopamine measured using the integral of the reduction peak. Data are fit to a Langmuir adsorption isotherm.

Adsorption Equilibria at PEDOT:Tosylate. To better understand the interaction of the analyte with the electrode we also plotted the surface coverage of dopamine by integrating the peak for both the oxidation and reduction waves (Figure 5C, D). It was found that the surface coverage at 1000 μM is not statistically different for the oxidation compared to the reduction (Student's t test, $p > 0.75$). This implies that there is the same amount of material present for both the forward and reverse scans. Both data sets were fit to a Langmuir adsorption isotherm (Figure 5C,D), which can be described as

$$\Gamma_{DA} = \frac{\Gamma_{max}\beta C}{1 + \beta C} \quad (3)$$

where Γ_{DA} is the surface coverage of dopamine, Γ_{max} is the maximum surface coverage, β is the adsorption strength, and C is the concentration of analyte in solution. At low concentrations ($\beta C \ll 1$), this term reduces to a linear form where the slope is the product of Γ_{max} and β, which we will call the sensitivity (b).[52] Using the oxidation peak, b was found to be 2.7×10^{-3} cm, and for the reduction peak, it was found to be 2.4×10^{-3} cm. These values are lower than a CFME, but the total surface coverage is much higher.[27,52,53] Because the adsorption strength of the analyte is not particularly high, this suggests that the analyte is not able to diffuse away from the electrode quickly. This observation supports the idea of analyte intercalation into the electrode. This interaction could potentially be exploited for applications that would benefit from a preconcentration such as fast-scan controlled-adsorption voltammetry[52] and other applications that already use PEDOT but would benefit from minimizing the capacitance such as solar cells, flexible electronics, and coatings for implantable sensors.[3,17,35]

CONCLUSIONS

The results presented here demonstrate that the vapor-phase synthesis of PEDOT:tosylate results in lower apparent capacitance than other methods. An apparent capacitance of 197 ± 7 μF/cm^2 is maintained up to a scan rate of 100 V/s. By using this synthesis coupled with standard photolithography techniques, it is possible to pattern microelectrodes or arrays composed of PEDOT:tosylate. These microelectrodes are thin, highly conductive, and capable of making rapid electrochemical measurements of relevant neurotransmitters. This photolithography process does not alter the apparent capacitance or the electroactive area of the PEDOT:tosylate film. Using these microelectrodes, we were able to demonstrate the first FSCV measurements at a polymer electrode using ferrocene carboxylic acid and, more biologically relevant, dopamine. When using the reduction peak for the detection of dopamine, these electrodes have a sensitivity of 3.7 ± 0.8 nA/μM and a submicromolar LOD. Interestingly, the reduction peak is much larger than that observed at carbon-fiber microelectrodes. Future experiments will need to be done to determine the chemical selectivity, lifetime, and temporal resolution of this electrode material before it can be used as an implantable biosensor. Furthermore, the unique surface chemistry that governs dopamine adsorption/intercalation into the polymer electrode could be used to make direct measurements of neurotransmitters.

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Notes

The authors declare the following competing financial interest(s): Dr. Michael Heien declares an actual or potential financial conflict of interest and is co-founder/equity holder in Knowmad Technologies, a licensee of University of Arizona (UA) intellectual property used in this research. This relationship has been disclosed to the UA Institutional Review Committee and is managed by a Financial Conflict of Interest Management Plan.

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