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Bipolar Electrochemical Measurement of Enantiomeric Excess with Inherently Chiral Polymer Actuators

Serena Arnaboldi, Gerardo Salinas, Giorgia Bonetti, Roberto Cirilli, Tiziana Benincori, and Alexander Kuhn*

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ABSTRACT: Straightforward enantioselective analytical methods are very important for drug safety, considering that in certain cases one of the two enantiomers of a chiral molecule might be harmful for humans. In this work, we propose a simple system for the direct and easy read-out of the enantiomeric excess of 3,4-dihydroxyphenylalanine (DOPA) as a model analyte. A conducting oligomer, i.e. oligo-(3,3′-dibenzothiophene), bearing inherently chiral features, is electrogenerated on a polypyrrole film. The resulting freestanding hybrid material is used as a wireless enantioselective actuator in a bipolar electrochemical cell. Combining in a single setup two individual actuators with opposite chiral features allows a direct visual read-out of enantiomeric excess, as the bending amplitude of each of the two actuators is directly correlated with the concentration of the corresponding stereoisomer of the analyte. Optimization of the experimental parameters results in efficient bending, giving access to the percentage values of the enantiomeric excess in mixtures containing different ratios of the antipodes, thus opening the way to potential applications for chiral in situ analysis.

KEYWORDS: Electrochemical Actuators, Direct Enantiomeric Excess Determination, Inherent Chirality, Absolute Enantiodiscrimination, Bipolar Electrochemistry

INTRODUCTION

Improvement of life quality has stimulated considerable research in drug safety. To reach this target, sensitive, enantioselective, and fast analytical methods are necessary. Electrochemical approaches often fulfill this scope. In classic electrochemical transduction, the detector electrode has to be wired to the power supply. Bipolar electrochemistry (BPE) is an interesting alternative, allowing direct electrochemical detection in a wireless way. This method is based on the use of two feeder electrodes and a conducting object (the bipolar electrode), placed in a solution containing supporting electrolyte. The potential difference between the electrolyte and the bipolar electrode drives asymmetric faradaic reactions (reduction/oxidation) at the cathodic and anodic extremities of the object. BPE has been used in the field of electrosynthesis and in photoelectrochemical cells, electrochemical reactors, and batteries. Recently, BPE has gained considerable attention for analytical purposes such as preconcentration, separation, electrochemical sensing and optical detection. For example, Klett et al. coupled bipolar electrochemistry with capillary electrophoresis for the potentiostat-less detection of an iron-based redox couple. In addition, BPE can be employed in combination with impedance spectroscopy and spectroelectrochemistry to develop new sensors. Among all of these methods, characterized by optical or electrochemical readouts of the transduced information, mechanical deformation of a wireless actuator is an extremely easy way to visualize the occurrence of redox processes in a straightforward way. Therefore, if the mechanical deformation, occurring during the bipolar experiment, is combined with chiral recognition, the concept can contribute to the development of new analytical techniques with an added value.

Bipolar electrochemical processes endowed with enantioselectivity have been previously proposed. A chiral imprinted mesoporous platinum film was combined with polypyrrole in a hybrid material, for which the preferential reaction with one enantiomer was detected by a differential electromechanical deformation of the polymer. The relative difference in bending was used as a sign of enantioselectivity, as it is based on a difference in local current intensity. However, a discrim-
ination only in terms of current amplitude has some limitations, e.g., the impossibility to distinguish between two enantiomers of the same molecule if they coexist in the same solution.\textsuperscript{27,28} Thus, it would be preferable if two enantiomers were also able to induce thermodynamic signal differences. In this context, an alternative approach was recently proposed, involving a particular type of chirality, intrinsic to the whole material, named inherent chirality. Compounds endowed with inherent chirality are characterized by the presence of an atropoisomeric scaffold or a helix unit. Furthermore, since inherently chiral molecules are endowed with $C_3$ symmetry,\textsuperscript{29,30} they have free homotopic positions, suitable for oligomerization, guaranteeing the full regioregularity of the synthesized macromolecular materials. Circular dichroism experiments demonstrated that inherent chirality is fully transferred from the monomer to the oligomer.

When this kind of compound is electrochemically deposited in an enantiopure form on a bulk electrode and tested in an electrochemical setup in the presence of chiral drugs, thermodynamically different voltammetric results are obtained. Well-defined signals with different peak potentials for each enantiomer of the chiral probe can be observed. The potential shift is due to energetically different situations for the two enantiomers on an inherently chiral electrode surface.\textsuperscript{31} This discrimination power of such chiral electrode surfaces has also been confirmed in the presence of unbalanced mixtures of enantiomers of chiral drugs, with the possibility to determine enantiomeric excess by recording the voltammetric signal.\textsuperscript{29,31}

An analog concept has also been used in combination with bipolar electrochemistry.\textsuperscript{32,33} The synergy between inherent chirality and the electromechanical properties of polypyrrole (Ppy)\textsuperscript{34–37} enabled the development of a bipolar electroactuator with a chirality-dependent on–off behavior. The enantiopure inherently chiral oligomer was deposited at one extremity of a Ppy strip and used as a bipolar electrode, reacting differently, with a yes–no response to the presence of the two enantiomers of a redox-active chiral analyte. The observed actuation is proportional to the concentration of the “good” enantiomer, whereas its antipode does not induce any actuation. In the present work, we further explore this concept of chiral bipolar electrochemistry by developing an on–off sensor able to detect directly and quantitatively the enantiomeric excess in unbalanced mixtures containing different ratios of the enantiomers of a model analyte (L- or D-3,4-dihydroxyphenylalanine, L- or D-DOPA).

### EXPERIMENTAL SECTION

#### Synthesis of the Hybrid Films

For the electrosynthesis of Ppy, a solution of pyrrole monomer (0.2 M, Sigma-Aldrich) was dissolved in an aqueous dodecylbenzenesulfonate (0.25 M, Sigma-Aldrich) solution. Two gold-coated glass slides were positioned parallel in a beaker filled with 12 cm$^3$ of this solution. These gold-coated glass slides were used as a working and counter electrode, whereas Ag/AgCl (3 M KCl) was the reference electrode. A fixed current of 4 mA was applied for 1.5 h for the polymerization of pyrrole. After polymerization, the Ppy film was washed with water, dried, and peeled off to be used as a support for the further oligomerization of the chiral monomer, i.e., 2,2′-bis[2-(5,5′-bithienyl)-3,3′-bithianaphthene (BT$^2$T$_4$)] (Figure 1a). The electro-synthesis of enantiopure oligo-(S)-BT$^2$T$_4$ and oligo-(R)-BT$^2$T$_4$ was carried out with the polypyrrole substrate acting as the working electrode in a small beaker containing 5 cm$^3$ of 0.1 M lithium perchlorate (LiClO$_4$) solution in acetonitrile (MeCN) and the (R)- or (S)-enantiopure monomers at 5 mM concentration. A platinum grid and a Ag/AgCl electrode were used as counter and reference electrodes, respectively. Considering that the total length of the self-standing film was around 2 cm, only a fraction of 1 cm of the Ppy has been dipped in the solution for further modification with the oligomers. Oligo-(S)-BT$^2$T$_4$ and oligo-(R)-BT$^2$T$_4$ were synthesized by chronopotentiometry at a fixed current value of 2 mA for 40 min. After the deposition, the oligo-(3,3′-dibenzo thiophene)–polypyrrole hybrid films were cut into strips of different geometry to be used as chiral sensors. The PPy film has a thickness comprising between 60 and 70 μm and the enantiopure thin oligomer layer of about 1 μm. Experimental details of the elaboration of the hybrid films are illustrated in Scheme S1.

#### Differential Pulse Voltammetry (DPV) Experiments

DPV experiments were carried out in an electrochemical cell, containing the enantiomers of L- or D-DOPA (5 mM) dissolved in an aqueous 0.2 M LiClO$_4$ solution. A platinum grid and a Ag/AgCl electrode were used as counter and reference electrodes, respectively. The hybrid electrode, composed of an oligo-(S)- or oligo-(R)-BT$^2$T$_4$ layer, deposited on a freestanding Ppy film was used as the working electrode. The optimized DPV parameters for recording the voltammetric signals of L- or D-DOPA were as follows: step potential 10 mV, modulation amplitude 60 mV, modulation time 40 ms, and interval time 200 ms.

#### Enantiomeric Excess Measurements

For the enantiomeric excess determination by bipolar electrochemistry, enantiopure (R)- or (S)-oligo-(3,3′-dibenzo thiophene)–polypyrrole hybrid films (15 or 17 mm long and with 0.06 or 0.03 mm$^2$ cross-sectional area) were fixed on the two opposite sides of a rectangular-shaped support in the center of the bipolar cell. The fraction of the strip that was fixed at the support was 8 mm long in all cases. Two graphite feeder electrodes were positioned at the extremities of the cell (5 cm apart, Figure S1). An aqueous 0.2 M LiClO$_4$ solution was used as supporting electrolyte to provide a sufficient amount of ions for charge compensation in the conducting polymer during the bipolar actuation in the presence of unbalanced mixtures of the two antipodes of DOPA. The analyzed D- DOPA/L- DOPA or D-DOPA were added separately at a concentration of 5 mM. The degree of bending of the actuator was recorded using a macroscope (LEICA Z16 APO) in video mode. Movie data treatment was carried out with ImageJ software.

#### Polypyrrole Resistance Measurements

The resistance of the Ppy cantilevers was measured by means of a digital multimeter. Four different strips of the hybrid materials were
cut with different geometries: (i) length of the Ppy strip 9 mm (total length 17 mm), cross-sectional area of 0.06 mm²; (ii) length of the Ppy strip 9 mm (total length 17 mm), cross-sectional area of 0.03 mm²; (iii) length of the Ppy strip 3 mm (total length 11 mm), cross-sectional area of 0.03 mm²; (iv) length of the Ppy strip 9 mm (total length 17 mm), cross-sectional area of 0.06 mm²; with nail varnish covering the Ppy cantilever starting 3 mm away from the support until the end of the strip. The thickness of the films was in all four cases around 60 μm. Bipolar measurements were carried out in this case by fixing only one strip of the hybrid material on the support, positioned in an aqueous 5 mM l-DOPA and 0.2 M LiClO₄ solution. The applied electric field was the same in all four cases (0.6 V cm⁻¹). The degree of actuation was recorded using a macroscope (LEICA Z16 APO) in video mode. Movie data treatment was carried out with ImageJ software.

RESULTS AND DISCUSSION

The experimental setup, including the actuation mechanism, is illustrated in Scheme 1 and Figure S1. The bipolar device

Scheme 1. Schematic Illustration of the Setup Used for the Wireless Enantiomeric Excess Detection of Mixtures of l- and d-DOPA before and after Applying the Electric Field

“The red cube represents the inert support on which the hybrid strips are fixed. The orange part represents the (S)-BT₂₅T₄ oligomer (the corresponding counterpart modified with (R)-BT₂₅T₄ oligomer is hidden at the backside of the inert support), whereas blue symbolizes the Ppy film. The actuation mechanism involves the selective oxidation of l- and d-DOPA on the two enantiopure oligomer-modified extremities and the reduction of Ppy, accompanied by bending induced by the cation uptake.

consists of two individual hybrid polymer strips, facing each other and being fixed on an inert support (red). The polymer strips are composed of enantiopure (R)- or (S)-oligomers (orange) electrodeposited on Ppy (blue). Under the influence of an electric field of 0.6 V cm⁻¹, the composite bipolar electrodes are polarized with respect to the surrounding solution, generating δ⁺ and δ⁻ extremities. At the δ⁺ side, electro-oxidation of l- or d-DOPA can take place on the enantiopure oligomer surface. At the δ⁻ extremity, Ppy is reduced, accompanied by the insertion of cations, in order to maintain electroneutrality, leading to a swelling of the polymer. The electroosynthesis of the Ppy strip was carried out on a flat electrode, meaning that, after peeling off the freestanding film from the substrate, the film presents one smooth face (the one in contact with the electrode surface) and a rough face (the one directed toward the electrolyte). The chiral oligomer was deposited on the smooth part of the polypyrrole. During the reduction of Ppy, cations enter the polymer preferentially at the rough face of the film. Since in the present setup the rough side of the film is facing inward, the uptake of cations will induce a significant bending of the cantilever in the opposite outward direction.

The inherently chiral oligomer employed in the selective electro-oxidation is a molecule with a bibenzothiophene as the central core (Figure 1A). The high racemization barrier allows separating the molecule into enantiomers, which are stable at room temperature.

As a preliminary test, we performed enantiorecognition measurements by means of differential pulse voltammetry, using as a working electrode a hybrid freestanding film constituted by Ppy and a (S)-oligomer layer, in the presence of either individual 5 mM L- or D-DOPA solutions or a DOPA racemate solution (total concentration of 10 mM). The DPV experiments show a clear separation in terms of oxidation potential when comparing the two enantiomers of the analyte (Figure 1B). The voltametric signals of l- and d-DOPA, when analyzed separately, show a peak-to-peak separation of around 300 mV. L-DOPA (green line) is preferentially oxidized by (S)-BT₂₅T₄, and consequently, the reaction of the d analyte (red line) is less favorable. The specular experiment employing (R)-BT₂₅T₄ as a chiral selector is illustrated in Figure S2. The yellow line represents the oxidation obtained on the (S)-oligomer when the racemate is present in solution. This illustrates the possibility to detect and discriminate both DOPA enantiomers, even when they are present simultaneously in the solution.

Before proceeding with the enantiomeric excess detection by bipolar electrochemistry, the operating conditions were optimized by employing hybrid film strips with different geometries in order to maximize the bending of Ppy and to find an easy and intuitive way to read-out the enantiomeric excess. A system with only one strip of the hybrid film (the bipolar electrode) has been prepared, composed of Ppy and (S)-oligomer, fixed to the red support (Figure 2), and placed in the center of a cell containing an aqueous solution of 5 mM l-DOPA in 0.2 M LiClO₄. An electric field of 0.6 V cm⁻¹ was applied for recording the actuation of the modified Ppy cantilever. Three actuators with different geometric features have been prepared: (A) length of the free Ppy strip 9 mm (total length 17 mm), cross-sectional area: 0.06 mm²; (B) length of the free Ppy strip 9 mm (total length 17 mm), cross-sectional area: 0.03 mm²; (C) length of the free Ppy strip 3 mm (total length 11 mm), cross-sectional area: 0.03 mm². The thickness of the film was identical (60 μm) in all three cases.

Figure 2 illustrates schematically the bending of the bipolar cantilever (left column) together with a superposition of the initial and last frame of a video recording of the bending experiments (right column). The bending behavior of the Ppy cantilever strongly depends on its geometry, which is most likely related to its internal resistance. For a long cantilever (9 mm) with a rather high cross-sectional area of 0.06 mm², the resistance of the polymer is 1.3 kΩ and the bending occurs like in a classic bipolar setup, as illustrated in Figure 2A. However, when the strip has the same length (9 mm) but a smaller cross-sectional area (0.03 mm²), the resistance of Ppy is 4.8 kΩ, and the actuation occurs only along the first 3 mm of the Ppy cantilever, leaving the remaining part of the polymer...
straight (Figure 2B). According to the general equation that correlates the resistance values to the geometrical parameters and the resistivity of an object \( R = \rho L / A \), where \( \rho \) is the resistivity of the material, \( L \) the length of the object, and \( A \) its cross-sectional area, we can observe an increase of the resistance as the value of the cross-sectional area decreases.

Thus, the electrons generated from the selective oxidation of DOPA at the \( \delta^+ \) extremity have to overcome this resistance in order to react at the opposite extremity of the Ppy cantilever. For a too high resistance, the potential drop across the resistance prevents the reduction reaction to occur at the end of the cantilever, and the electrons react instead preferentially at the beginning of the freestanding film. This results in a straight part of the Ppy strip, indicating that this section is not electroactive.

To confirm this hypothesis, the experiment depicted in Figure 2C has been performed. A strip with the same cross-sectional area as the one of Figure 2B (0.03 mm\(^2\)), but with a shorter cantilever (3 mm), was used. The resistance value is 0.4 k\( \Omega \), in agreement and as expected for the shorter Ppy strip. Actuation occurs in the classic way since the small potential drop does not prevent the electrons from reacting at the end of the hybrid film. To mimic the behavior of the cantilever in Figure 2B, but with the same geometrical features as the one of Figure 2A, a Ppy hybrid film with a length of 9 mm and a cross-sectional area of 0.06 mm\(^2\) has been prepared, covering the strip with nail varnish starting 3 mm away from the support until the end. In this way, the electron flow through this part of the polymer is inhibited, and bending occurs only in the first part of the Ppy strip (Figure S3).

After these preliminary optimization experiments, bipolar electrochemistry was used for detecting the enantiomeric excess. In Figure 3, each sensor is constituted by two individual strips of the composite films, Ppy + (S)-oligomer and Ppy + (R)-oligomer, fixed on the red support and placed in a racemic solution of 5 mM L-DOPA + 5 mM D-DOPA in 0.2 M LiClO\(_4\).
After an electric field of 0.6 V cm$^{-1}$ is applied, the cantilevers bend in both cases with a final amplitude that can be directly correlated with the enantiomeric ratio of the solution. Since the analyzed mixture is a racemate, the actuation of the Ppy film is in both cases symmetric with respect to the barycenter of the red support. More precisely, the (R)-oligomer-modified arm selectively oxidizes D-DOPA, and the (S)-oligomer-modified part exclusively reacts with L-DOPA. However, the type of bending is different for columns A and B, due to the different cross-sectional areas (vide supra). Even though the bending amplitude can be converted in both cases into identical enantiomeric ratios (∼50:50) by measuring the relative deflection of the two arms, the bending obtained for A seems to be more convenient to determine enantiomeric excess in a straightforward way (Video S1). This holds not only for the case of a racemate but also in other cases when the ratio between the two enantiomeric probes is different. Since bending occurs only in the first part of the strip, one can easily calculate the percentage of actuation by measuring the maximum distance between the left side of the red support and the final position of the extremity of the hybrid film modified with the (R)-oligomer; the same procedure can also be used for the right side where the (S)-hybrid strip is attached. Enantiomeric excess values can then be calculated by dividing the difference between the individual maximum distances by the total deflection of the two polymer arms.

Based on these findings, we decided to use for all subsequent experiments the cantilever geometry of Figure 3A. In particular, the following molar ratios between D- + L-DOPA and L-DOPA were analyzed: 0:10, 3:7, 5:5, and 7:3 by maintaining constant the total concentration of D- + L-DOPA (10 mM). In principle, lower concentrations might also be used; however, below 2 mM, bending is less well pronounced. For the case of 5:0 and 0:5, L-DOPA and D-DOPA were analyzed separately in 5 mM solutions. The corresponding measured enantiomeric excess values are indicated in Figure 4. They are in very good agreement with the relative concentrations of L- and D-DOPA in each solution. When only L-DOPA is present at 10 mM concentration and the (R)-BT$_2$T$_4$ oligomer is deposited on both Ppy strips, no actuation is observed as the hybrid film modified with the (R)-oligomer is attached. Enantiomeric excess values can then be calculated by dividing the difference between the individual maximum distances by the total deflection of the two polymer arms.

**CONCLUSION**

The concept of bipolar electrochemistry was successfully used for the measurement of enantiomeric excess of unbalanced mixtures of L- and D-DOPA as a model analyte. Two hybrid Ppy films, modified with oligomers bearing opposite intrinsic chiral features, were used simultaneously as bipolar electrodes. The actuation efficiency was optimized by adapting the geometry of the freestanding polymer films serving as cantilevers. The respective degree of actuation was found to be directly correlated with the concentration of the chiral analyte molecules in solution, even when they are present as a mixture. This enables the selective measurement of enantiomeric excess of chiral probes from a qualitative and quantitative point of view. This opens up the perspective to use this technique for the analysis of real samples in the frame of chiral technologies, with the inherent advantage of a bipolar electrochemistry setup that one can build a whole array of such sensing devices, powered by just one pair of feeder electrodes.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmeasuresciau.1c00011.

Additional experimental scheme, photograph of the experimental setup, differential pulse voltammetry of the (R)-BT$_2$T$_4$ oligomer in the presence of DOPA enantiomers, and bipolar behavior of an actuator covered by nail varnish (PDF)

Actuation of a Ppy cantilever in a solution of DOPA racemate (10 mM) (MP4)

Actuation of a Ppy cantilever in a solution of D- + L-DOPA with a 3:7 molar ratio and for the case of the specular 7:3 mixture (MP4)

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Author Contributions
S.A. designed and performed experiments and wrote and edited the manuscript. G.S. designed the bipolar cell and edited the manuscript. A.K. proposed the research project, provided resources, designed experiments, and edited the manuscript. T.B. designed the inherently chiral monomers. G.B. synthesized the inherently chiral monomers, and R.C. separated the enantiomers of the inherently chiral monomers by chiral HPLC.

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Notes
The authors declare no competing financial interest.

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ABBREVIATIONS
BPE, bipolar electrochemistry; DPV, differential pulse voltammetry; Ppy, polypyrrol; DOPA, dihydroxyphenylalanine; LiClO\textsubscript{4}, lithium perchlorate; MeCN, acetonitrile; BT\textsubscript{2}T\textsubscript{4}, 2’-bis[2-(5,2’-bithienyl)]-3,3’-bithianaphthene

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