

Boc-phenylalanine Grafted Poly(3,4-propylenedioxythiophene) Film for Electrochemically Chiral Recognition of 3,4-Dihydroxyphenylalanine Enantiomers

Jun-Long Niu^a, Ke-Ke Chai^a, Mei-Xing Zeng^a, Tian-Tian Wang^a, Chun-Yan Zhang^a, Shuai Chen^{a*}, Jing-Kun Xu^{a,b*}, and Xue-Min Duan^{a*}

^a Jiangxi Provincial Key Laboratory of Drug Design and Evaluation, School of Pharmacy, Jiangxi Science & Technology Normal University, Nanchang 330013, China

^b School of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, China

Abstract To prepare chiral monomer with single chiral center and higher stereospecificity, a pair of amino-functionalized chiral 3,4-propylenedioxythiophene (ProDOT) derivatives, chiral (3,4-dihydro-2*H*-thieno[3,4-*b*][1,4]dioxepin-3-yl)methyl 2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate (ProDOT-Boc-Phe), were synthesized. Chiral poly[(3,4-dihydro-2*H*-thieno[3,4-*b*][1,4]dioxepin-3-yl)methyl 2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate] (PProDOT-Boc-Phe) modified electrodes were synthesized *via* potentiostatic polymerization of chiral ProDOT-Boc-Phe. Chiral PProDOT-Boc-Phe films displayed good reversible redox activities. The enantioselective recognition between chiral PProDOT-Boc-Phe modified glassy carbon electrodes and DOPA enantiomers was achieved by different electrochemical technologies, including cyclic voltammetry (CV), square wave voltammetry (SWV), and differential pulse voltammetry (DPV). (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe showed higher peak current responses toward L-DOPA and D-DOPA, respectively.

Keywords Chiral conducting polymer; Amino acids; Chiral sensors; 3,4-Dihydroxyphenylalanine; Electrochemistry

Citation: Niu, J. L.; Chai, K. K.; Zeng, M. X.; Wang, T. T.; Zhang, C. Y.; Chen, S.; Xu, J. K.; Duan, X. M. Boc-phenylalanine grafted poly(3,4-propylenedioxythiophene) film for electrochemically chiral recognition of 3,4-dihydroxyphenylalanine enantiomers. *Chinese J. Polym. Sci.* 2019, 37, 451–461.

INTRODUCTION

In human body, most biological molecules have chiral structure and show extreme stereospecificity to chiral drug enantiomers.^[1] Chiral drugs usually have at least one pair of optical enantiomers. In many instances, only one enantiomer of these chiral drugs is biochemically active, while the other enantiomer is inactive or even toxic.^[2] For example, L-dihydroxyphenylalanine (L-DOPA) has an evident treatment effect for Parkinson's disease. However, D-dihydroxyphenylalanine (D-DOPA) has no treatment effect on Parkinson's disease. D-DOPA will accumulate in human body and give an unnecessary burden to patients.^[3,4] Therefore, it is necessary to develop a convenient method for differentiating enantiomers.

Classically, a number of techniques have been used for chiral recognition, which can be split into three categories: spectroscopy, chromatography, and sensor methods.^[5–7]

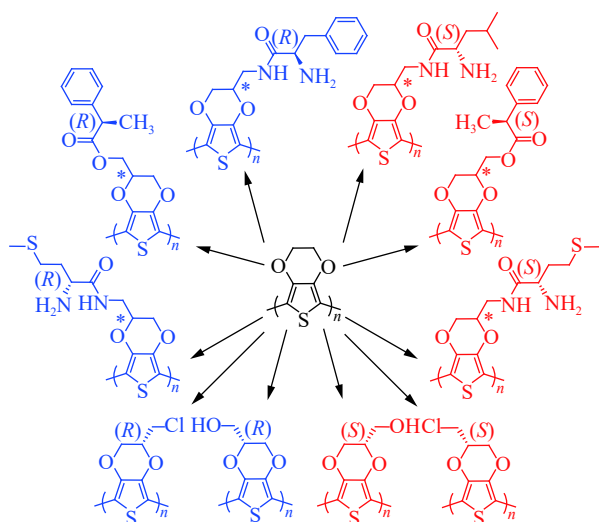
Spectroscopy methods mainly include nuclear magnetic resonance (NMR)^[8] and circular dichroism spectroscopy (CD).^[6] Chromatography methods mainly include high performance liquid chromatography (HPLC),^[7] gas chromatography (GC),^[9] and capillary electrophoresis (CE).^[10] The spectroscopy and chromatography methods have higher efficiency and accuracy. However, they need to be equipped with expensive instruments, and the operation is time-consuming and with much complexity. Compared with the methods mentioned above, electrochemical chiral sensors have lower cost, higher sensitivity, and can be operated and maintained easily, thus attracting more and more attention.^[11,12] Chiral electrode materials with unique properties are very important to the chiral electrochemical sensors.

With unique π orbital structure, conducting polymers are sensitive to the alterations of chain conformation.^[13] When the chain conformation of conducting polymers is perturbed, chiral conducting polymers can convert the perturbations to fast and sensitive electrical signals.^[14] Moreover, the thickness of the deposited conducting polymers layer can be controlled. Thus, conducting polymers have been considered as promising electrode materials for chiral electrochemical sensors.^[15] With outstanding stability, high conductivity, and

* Corresponding authors: E-mail chenshuai@ms.xjb.ac.cn (S.C.)
E-mail xujingkun@jxstnu.edu.cn (J.K.X.)
E-mail duanxuemin@126.com (X.M.D.)

Received October 15, 2018; Accepted December 11, 2018; Published online January 14, 2019

By attaching chiral functional groups to the backbone of PEDOT, many chiral PEDOT derivatives have been synthesized. Based on the transesterification of 3,4-dialkoxythiophenes and chiral 1,2-diols, Caras-Quintero and Bäuerle reported a variety of chiral disubstituted PEDOT derivatives.^[17] Akagi *et al.* prepared a pair of copolymer-type chiral PEDOT derivatives, which were made up of EDOT and chiral phenylene as spacer.^[18] In our previous study, a series of EDOT-based chiral conducting polymers were synthesized by grafting chiral hydroxymethyl,^[19] chloromethyl,^[20] phenylpropionic acid,^[21] methionine,^[22] leucine,^[23] and phenylalanine.^[24] The chemical structures of the chiral EDOT derivatives are illustrated in [Scheme 1](#). However, when natural chiral molecules, namely amino acids, are introduced into the PEDOT chains, PEDOT derivatives have an extra chiral center in the ethylene bridge groups. It is difficult to obtain pure chiral enantiomers when monomer has an extra chiral center. In addition, the extra chiral center is detrimental to the formation of ordered structures, and could affect the stereoselective interactions between chiral electrochemical sensors and enantiomers. In order to resolve this problem, we have introduced hydroxymethyl^[19] and chloromethyl^[20] groups to the ethylene bridge segments to avoid extra chiral center. However, the steric hindrance of hydroxymethyl and chloromethyl was lower. Generally, the smaller steric effect the chiral center has, the lower stereospecificity the chiral conducting polymers perform. Therefore, it is necessary to prepare monomer with single chiral center and higher stereospecificity.



When introducing chiral groups into the propylene bridge groups of 3,4-propylenedioxythiophene (ProDOT), ProDOT derivatives cannot generate extra chiral center. Hence, the chiral ProDOT-based conducting polymer is considered as a substitute for EDOT-based conducting polymer.^[25,26] Amino

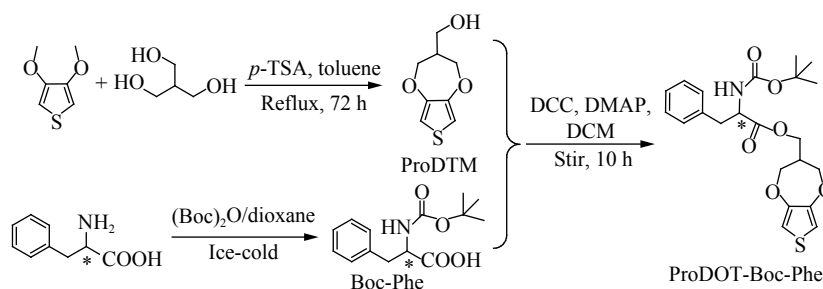
In this work, chiral Boc-phenylalanine, as the chiral functional group, was introduced into ProDOT by covalent bonding. A pair of chiral ProDOT derivatives, namely chiral (3,4-dihydro-2*H*-thieno[3,4-*b*][1,4]dioxepin-3-yl)methyl 2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (ProDOT-Boc-Phe) were synthesized for the first time. Then, the polymers were electrosynthesized in dichloromethane (DCM). Further, the circular dichroism, spectroscopic properties, morphology, and electrochemical behavior of the chiral PProDOT-Boc-Phe films were investigated. Finally, sensors based on chiral PProDOT-Boc-Phe were used to recognize DOPA enantiomers.

Materials

Synthesis of (D)-/(L)-ProDOT-Boc-Phe

(D)-ProDOT-Boc-Phe: ¹H-NMR (400 MHz, CDCl₃, δ, ppm): 7.26 (m, 5H), 6.51 (s, 2H), 4.99 (s, 1H), 4.59 (s, 1H), 4.29 (m, 2H), 3.99 (s, 4H), 3.09 (s, 2H), 2.35 (s, 1H), 1.42 (s, 9H).

(L)-ProDOT-Boc-Phe: $^1\text{H-NMR}$ (400 MHz, CDCl_3 , δ , ppm): 7.31 (m, 5H), 6.53 (s, 2H), 5.00 (s, 1H), 4.59 (s, 1H), 4.32 (m, 2H), 4.02 (s, 4H), 3.11 (s, 2H), 2.38 (s, 1H), 1.44 (s, 9H).



Scheme 2 The synthesis route to ProDOT-Boc-Phe

Synthesis of (D)-/(L)-PProDOT-Boc-Phe

Electrochemical polymerization was carried out using $0.01 \text{ mol} \cdot \text{L}^{-1}$ (D)-/(L)-ProDOT-Boc-Phe in DCM containing $0.1 \text{ mol} \cdot \text{L}^{-1}$ Bu_4NPF_6 with CHI 660D electrochemistry workstation. A three-electrode system, including a glassy carbon electrode (GCE) as a working electrode, an Ag/AgCl electrode as the reference electrode, and a platinum wire electrode as the counter electrode, was employed to polymerize (D)-/(L)-PProDOT-Boc-Phe.

In addition, to obtain a sufficient weight of PProDOT-Boc-Phe films for characterization, the ITO glasses with surface area of $2 \text{ cm} \times 2.5 \text{ cm}$ were served as working electrode and counter electrode, and the Ag/AgCl electrode was employed as the reference electrode.

Furthermore, GCE as a working electrode, an saturated calomel electrode (SCE) as the reference electrode, and a platinum wire electrode as the counter electrode, were employed to investigate the electrochemical stability, electroactivity, and chiral recognition ability of PProDOT-Boc-Phe.

Characterization

The structures of ProDOT-Boc-Phe were identified by means of a nuclear magnetic resonance spectrometer (NMR, Bruker AV-400, Switzerland). To identify the polymer structures, infrared spectra of the PProDOT-Boc-Phe were measured with Fourier-transform infrared spectrometer (FTIR, Bruker Vertex 70, Switzerland) with samples in KBr pellets from 400 cm^{-1} to 4000 cm^{-1} . Ultraviolet-visible (UV-Vis) spectra were recorded on a UV-Vis-near-infrared spectrophotometer (UV-Vis-NIR, Perkin-Elmer Lambda 900, USA). The chiroptical properties of chiral PProDOT-Boc-Phe films were measured with circular dichroism spectropolarimeter (CD, JASCO J-720, Japan). The morphology of PProDOT-Boc-Phe films was observed by scanning electron microscopy (SEM, JSM-6701F, Japan).

RESULTS AND DISCUSSION

Electrochemical Polymerization of (D)-/(L)-ProDOT-Boc-Phe

Because (D)-ProDOT-Boc-Phe and (L)-ProDOT-Boc-Phe exhibit high solubility in DCM, DCM containing $0.1 \text{ mol} \cdot \text{L}^{-1}$ Bu_4NPF_6 was chosen as the electrolyte systems for polymerization. The electropolymerization process of monomer and the redox process of their polymers were investigated by using successive cyclic voltammograms (CVs). As can be seen from Fig. 1, during the first anodic scan, the onset oxidation potentials (E_{onset}) of (D)-ProDOT-Boc-Phe and (L)-ProDOT-Boc-Phe were initiated at 1.52 and

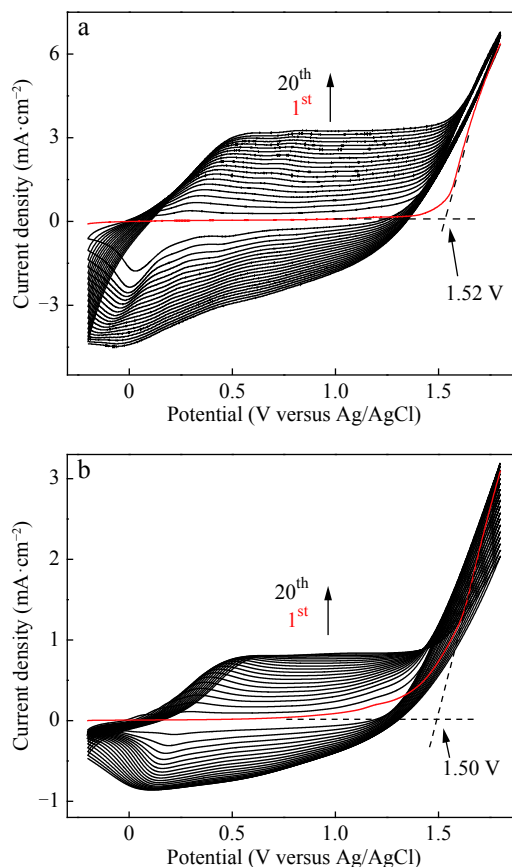


Fig. 1 Cyclic voltammograms of (a) (D)-ProDOT-Boc-Phe and (b) (L)-ProDOT-Boc-Phe in DCM containing $0.1 \text{ mol} \cdot \text{L}^{-1}$ Bu_4NPF_6 (The red line is the first sweep segment of cyclic voltammograms.)

1.50 V versus Ag/AgCl, respectively, which were higher than E_{onset} of EDOT-Boc-Phe (1.4 V versus Ag/AgCl).^[24] This phenomenon means that a high potential over 1.50 V versus Ag/AgCl was required to prepare chiral PProDOT-Boc-Phe films. The E_{onset} s of (D)-ProDOT-Boc-Phe and (L)-ProDOT-Boc-Phe have subtle difference, which might result from the different steric hindrance of chiral function group. As shown in Fig. 1, the increase of redox currents implied that the conductive PProDOT-Boc-Phe polymer was gradually formed on the surface of glassy carbon electrode (GCE). The potential shift of current peaks indicated that increased potential was needed to overcome the increased electrical resistance of PProDOT-Boc-Phe films. In addition, the redox peaks were caused by the oxidation/re-reduction (*p*-doping/dedoping) processes of ProDOT-Boc-Phe films.

Potentiostatic method was chosen to prepare PProDOT-

Boc-Phe films, and the applied potentials were optimized. As shown in Fig. 2, the current density was nearly zero when the potential was lower than E_{onset} . When the potential was higher than E_{onset} , the current density increased with the increasing potential. When the potential was too high, the current density decreased. This phenomenon occurred because of the positive correlation between the polymerization rate and the potential. Initially, the current density increased with the increased potential, but when the potential was too high, the polymerization proceeded very rapidly, and the electroactive material could not transfer to the glassy carbon electrode in time.[29] The concentration of the electroactive material around the working electrode decreased, and the monomer transformed into oligomers. After considering the factors that would influence the quality of the PProDOT-Boc-Phe films, such as the polymerization rate, morphology of polymer, and adhesive strength, an applied potential of 1.65 V versus Ag/AgCl was selected to electropolymerize ProDOT-Boc-Phe.

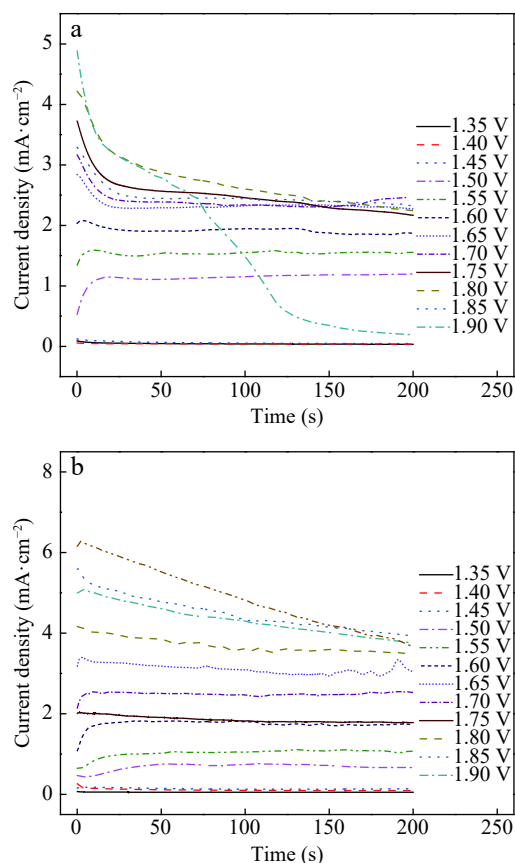


Fig. 2 Chronoamperometric curves of (a) $0.01 \text{ mol} \cdot \text{L}^{-1}$ (D)-ProDOT-Boc-Phe and (b) $0.01 \text{ mol} \cdot \text{L}^{-1}$ (L)-ProDOT-Boc-Phe on GCE at different potentials in DCM with $0.1 \text{ mol} \cdot \text{L}^{-1}$ Bu₄NPF₆ for 200 s

Structural Spectroscopic Characterization and Surface Morphology of (D)-/(L)-ProDOT-Boc-Phe

FTIR spectra of ProDOT-Boc-Phe and PProDOT-Boc-Phe are given in Fig. 3. The band of (D)-ProDOT-Boc-Phe at 3104 cm^{-1} and the band of (L)-ProDOT-Boc-Phe at 3108 cm^{-1} corresponded to the C—H vibration of 2- and 5-positions in the thiophene ring. However, these bands

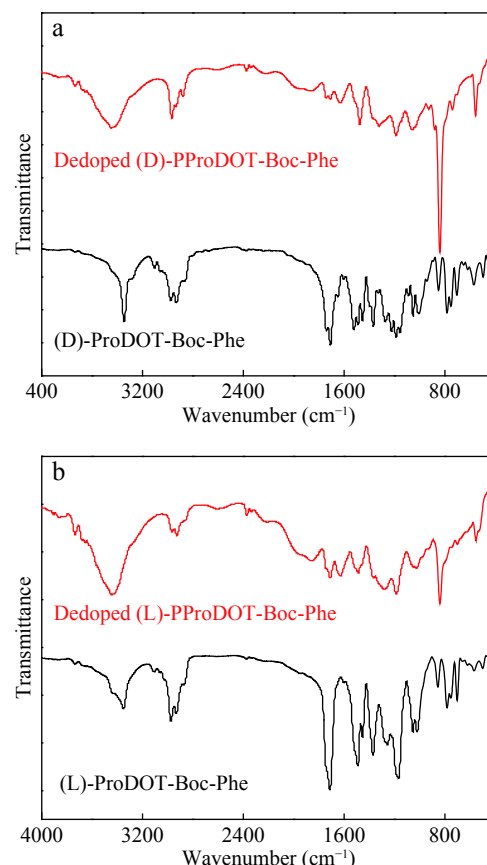


Fig. 3 FTIR spectra of (a) (D)-ProDOT-Boc-Phe and (b) (L)-ProDOT-Boc-Phe

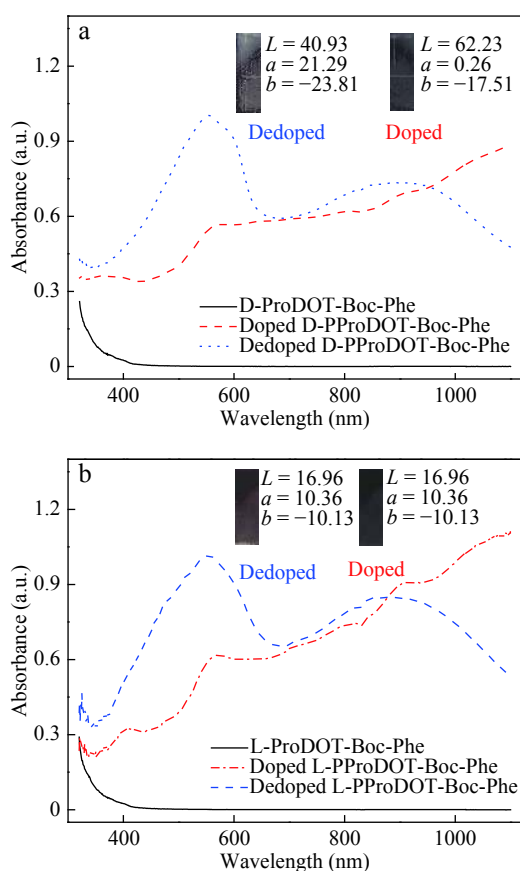
disappeared in the polymer spectrum. These spectral changes demonstrated the electrochemical polymerization occurred at the 2- and 5-positions in the thiophene ring.

The characteristic bands of ProDOT-Boc-Phe, for example, the skeletal vibration of the benzene ring at around $1560\text{--}1450 \text{ cm}^{-1}$, the asymmetrical stretching vibration and symmetrical stretching vibration of $-\text{CH}_3$ groups at 2930 and 2870 cm^{-1} , and the stretching vibration of $\text{C}=\text{O}$ of the ester group at 1735 cm^{-1} , still existed in the PProDOT-Boc-Phe spectrum. This evidence proved that the ester group was stable and the chiral function group was not changed. It is worth mentioning that the absorption bands in PProDOT-Boc-Phe spectra were broader than those in ProDOT-Boc-Phe spectra. One reason for this phenomenon is that the PProDOT-Boc-Phe films have different chain lengths. The vibrational modes of PProDOT-Boc-Phe films with different chain lengths exhibit different IR shifts. The bands of PProDOT-Boc-Phe films overlap one another, and lead to broader absorption bands in the IR spectra. The detailed band assignments and the comparison of ProDOT-Boc-Phe and PProDOT-Boc-Phe are summarized in Table 1.

As illustrated in Fig. 4, the spectra of chiral ProDOT-Boc-Phe have no characteristic absorption band at $300\text{--}1100 \text{ nm}$. However, dedoped PProDOT-Boc-Phe shows wide maximum absorption band at 553 nm , which is a result of the $\pi\text{--}\pi^*$ absorption transition.[30] It is generally accepted that the wavelength in UV-Vis spectra positively correlates with the conjugation length of the polymer. The difference between

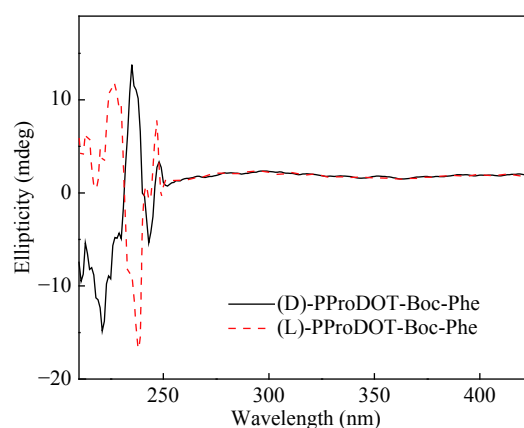
Table 1 Assignment of FTIR spectra of (D)-ProDOT-Boc-Phe, (L)-ProDOT-Boc-Phe, (D)-PProDOT-Boc-Phe, and (L)-PProDOT-Boc-Phe

Band (cm ⁻¹)				Assignment
(D)-ProDOT-Boc-Phe	(D)-PProDOT-Boc-Phe	(L)-ProDOT-Boc-Phe	(L)-PProDOT-Boc-Phe	
3104		3108		=C—H
2975	2967	2974	2973	CH ₃ v _{as}
2860	2870	2867	2870	CH ₃ v _s
1708	1710	1712	1710	C=O v
1654	1630	1615	1628	C=C v
1597, 1521, 1489, 1454	1474	1601, 1491, 1454	1487	benzene ring v
751, 704	739	782, 701	701	γ benzene ring
1367	1323	1369	1363	C—C v thiophene ring
1187	1186	1168	1185	C—H out-of-plane bending vibrations
1154	1059	1064	1024	C—O—C v
1007, 849	922, 839	1020, 866	838	C—S v

**Fig. 4** UV-Vis spectra of (a) (D)-ProDOT-Boc-Phe and (b) (L)-ProDOT-Boc-Phe films

ProDOT-Boc-Phe and PProDOT-Boc-Phe indicated that the polymerization of ProDOT-Boc-Phe has occurred. The wide maximum absorption band in UV-Vis spectra is consistent with the broader absorption bands in IR spectra, which confirmed that PProDOT-Boc-Phe films had broad chain length distribution.^[31] In addition, the color of chiral PProDOT-Boc-Phe changed from light-blue to black-blue when changing from a doped to a dedoped state.

In order to measure the chiroptical properties of the PProDOT-Boc-Phe films, circular dichroism (CD) spectra of (D)-/(L)-PProDOT-Boc-Phe were investigated. As can be seen from Fig. 5, CD spectra of (D)-/(L)-PProDOT-Boc-Phe show

**Fig. 5** CD spectra of PProDOT-Boc-Phe

mirror symmetry, which suggests that they were a pair of enantiomers. This phenomenon enabled chiral PProDOT-Boc-Phe to be used for electrochemically chiral sensor.

The morphologies of (D)-PProDOT-Boc-Phe (Fig. 6a) and (L)-PProDOT-Boc-Phe (Fig. 6b) films were investigated by SEM. (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe films were deposited on ITO glass. In the process of polymerization, the thickness of the polymer film was controlled by the total charge. As shown in Fig. 6, (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe had similar surface morphology. The porous structure of PProDOT-Boc-Phe was uniformly distributed and had similar size. Porous structures provide larger specific surface areas and stronger adsorption ability, which is quite important for chiral electrochemical sensors.^[20] The electrochemically effective surface area of PProDOT-Boc-Phe was determined by chronocoulometry using 0.1 mmol·L⁻¹ K₃[Fe(CN)₆] containing 1 mol·L⁻¹ KCl as a model complex, based on the Anson equation:^[32]

$$Q(t) = 2nFAcD^{1/2}t^{1/2}/\pi^{1/2} + Q_{dl} + Q_{ads} \quad (1)$$

where n is the electron transfer number, F is the Faraday constant, A is the electrochemically effective surface area, c is the concentration of the K₃[Fe(CN)₆], Q_{ads} and Q_{dl} are the Faradic charge and the double-layer charge, respectively. Other symbols have their usual meanings. As shown in Fig. 6(c), the linear regression equations of $Q-t^{1/2}$ curves on bare GCE, (D)-PProDOT-Boc-Phe, and (L)-PProDOT-Boc-Phe were $Q(\mu C) = 7.871 + 86.269t^{1/2}$ ($R^2 = 0.999$),

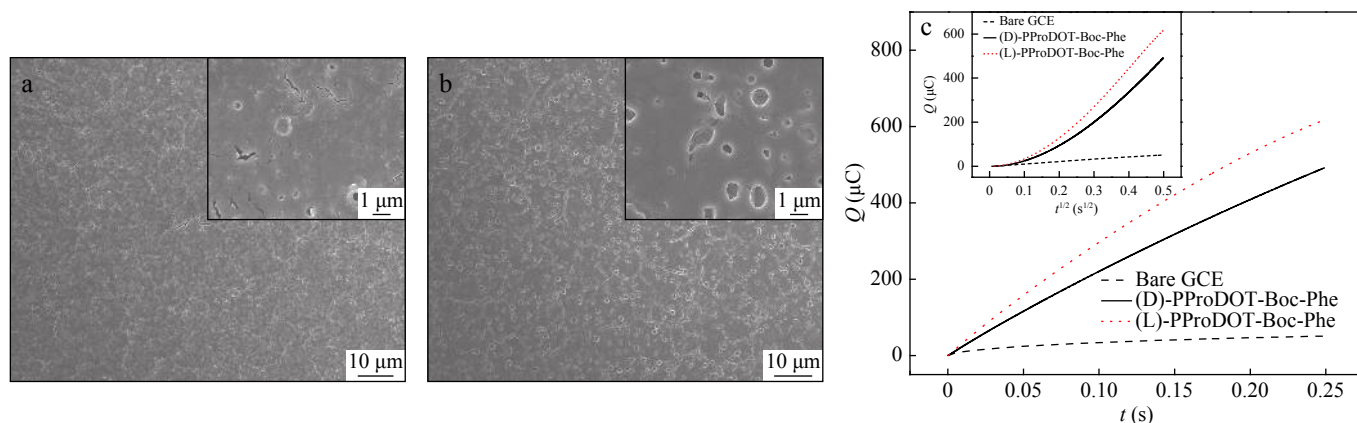


Fig. 6 SEM images of (a) (D)-PProDOT-Boc-Phe and (b) (L)-PProDOT-Boc-Phe films deposited electrochemically on ITO glasses (Magnification: 1000 $\times$, inset: 10000 $\times$); (c) Plot of Q - t curves of bare GCE, (D)-PProDOT-Boc-Phe, and (L)-PProDOT-Boc-Phe in 1 mmol·L⁻¹ K₃[Fe(CN)₆] containing 0.1 mol·L⁻¹ KCl. Inset: plot of Q - $t^{1/2}$ curves of bare GCE, (D)-PProDOT-Boc-Phe, and (L)-PProDOT-Boc-Phe

$Q(\mu\text{C}) = -310.337 + 1606.656t^{1/2}$ ($R^2 = 0.999$), and $Q(\mu\text{C}) = -219.612 + 1679.010t^{1/2}$ ($R^2 = 0.999$), respectively. According to the slopes of the linear relationship between Q and $t^{1/2}$, electrochemically effective surface area was calculated to be 0.288 cm² for bare GCE, 5.358 cm² for (D)-PProDOT-Boc-Phe, and 5.598 cm² for (L)-PProDOT-Boc-Phe. The electrochemically effective surface areas of PProDOT-Boc-Phe were 18 times larger than that of bare GCE. These results proved that the PProDOT-Boc-Phe with porous structure possessed a large surface area, which could enhance

the electrochemical response.

Electrochemistry Properties of (D)-/(L)-PProDOT-Boc-Phe

Through a series of CVs in DCM containing 0.1 mol·L⁻¹ Bu₄NPF₆ at different scan rates, the electrochemical stability and electroactivity of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe films were investigated. As shown in Fig. 7, the anodic and cathodic current densities of PProDOT-Boc-Phe were linearly dependent on the scanning rates,

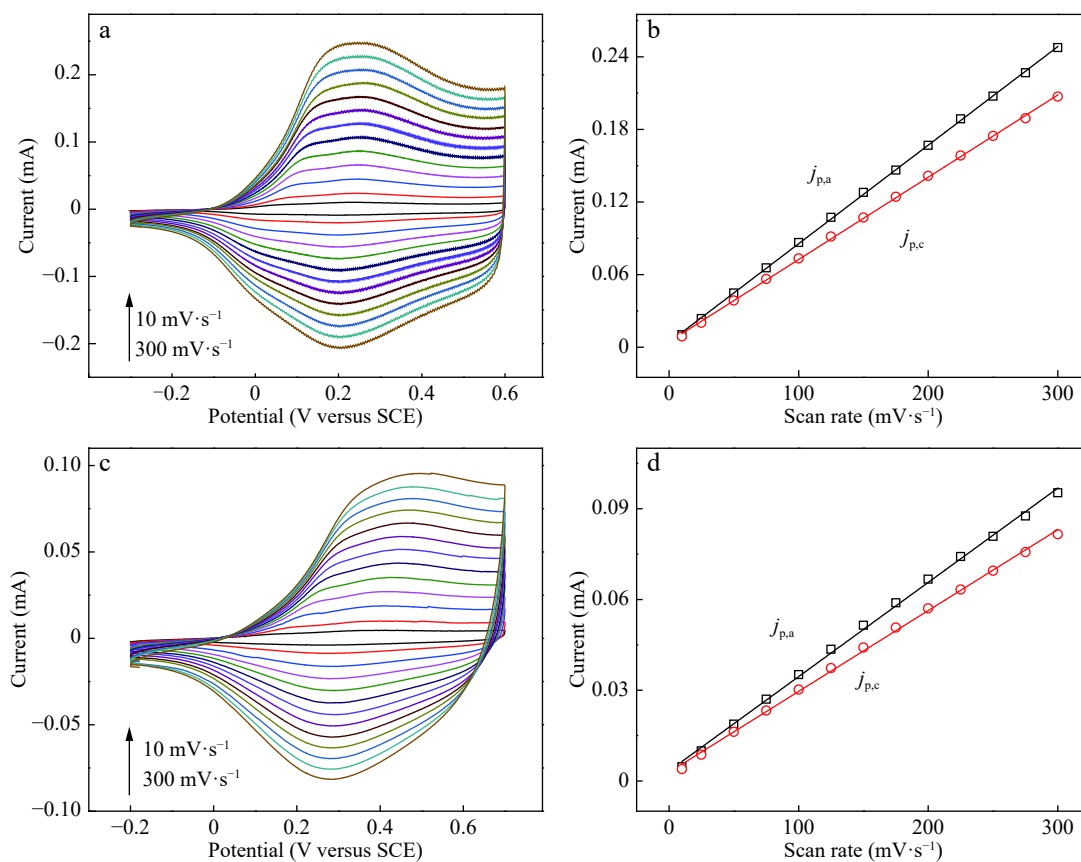


Fig. 7 CVs of (a) (D)-PProDOT-Boc-Phe and (c) (L)-PProDOT-Boc-Phe films at different potential scan rates, and redox peak current of (b) (D)-PProDOT-Boc-Phe and (d) (L)-PProDOT-Boc-Phe versus potential scan rates. The potential range is -0.2–0.7 V. $j_{p,a}$ and $j_{p,c}$ denote the anodic and cathodic peak current densities, respectively.

which indicated that the redox process of chiral PProDOT-Boc-Phe was non-diffusional.^[33] In addition, the peak potential of the PProDOT-Boc-Phe films had an obvious shift, which might be caused by the slow heterogeneous electron transfer, effects of local rearrangements of polymer chains, and slow mutual transformations of various electronic species. The electrochemical parameters of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe films are listed in Table 2.

The electrochemical stability of PProDOT-Boc-Phe was researched in 0.25 mol·L⁻¹ H₂SO₄ using a long-time CV method. As shown in Fig. 8, the electrochemical activities of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe were preserved at rates of 95% and 98% after 100 cycles, respectively. In addition, the electrochemical activities of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe retained 94% and 95% of the exchange charge after 500 cycles, respectively. Overall, both (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe experienced relatively high electrochemical stabilities, which is an important basis for chiral recognition.

Kinetic Interaction of (D)-/(L)-PProDOT-Boc-Phe

The kinetic interaction of PProDOT-Boc-Phe was investigated. The corresponding CVs of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe are shown in Figs. 9(a) and 9(b). The peak potential separations increased with the scan rates, indicating the limitation arising from charge transfer kinetics.^[33] As shown in Figs. 9(c) and 9(d), the anodic peak currents of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe were proportional to the scan rates over the range of 25–300 mV·s⁻¹ with linear regression equations:

$$I_{pa} = 35.420 + 0.821v, R^2 = 0.996, \text{ (D)-PProDOT-Boc-Phe}$$

$$I_{pa} = 70.067 + 0.990v, R^2 = 0.994, \text{ (L)-PProDOT-Boc-Phe}$$

These phenomena indicated the oxidations of DOPA were adsorption-controlled processes at those scan rates. As

shown in Figs. 9(e) and 9(f), the anodic peak potentials of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe were proportional to the natural logarithm scan rates with linear regression equations:

$$E_{pa} = 0.597 + 0.032 \ln v, R^2 = 0.990, \text{ (D)-PProDOT-Boc-Phe}$$

$$E_{pa} = 0.670 + 0.031 \ln v, R^2 = 0.992, \text{ (L)-PProDOT-Boc-Phe}$$

Based on Laviron's Eq. (2),^[34] the charge transfer coefficient (α) can be determined by measuring the slopes of E_{pa} versus natural logarithm scan rate:

$$E_{pa} = E^0 + \frac{RT}{\alpha nF} \ln \left(\frac{RTk_s}{\alpha nF} \right) + \frac{RT}{\alpha nF} \ln v \quad (2)$$

where α is charge transfer coefficient, F is the Faraday constant (96485 C·mol⁻¹), R is molar gas constant (8.314 J·mol⁻¹·K⁻¹), T is temperature (298 K). Considering two electrons transferred for DOPA, α of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe were obtained. Charge transfer coefficients of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe were 0.401 and 0.414, respectively. Substituting the α values and the scan rate of 100 mV·s⁻¹ into the following Eq. (3):^[35]

$$\lg k_s = \alpha \lg(1 - \alpha) + (1 - \alpha) \lg \alpha - \lg \frac{RT}{nFv} - \frac{\alpha(1 - \alpha)nF\Delta E_p}{2.303RT} \quad (3)$$

the electron transfer rate constants (k_s) of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe were calculated to be 0.860 and 0.834 s⁻¹, respectively.

Chiral Recognition Properties of (D)-/(L)-PProDOT-Boc-Phe

Referring to other publications,^[36] 0.25 mol·L⁻¹ H₂SO₄ (pH = 0.6) was selected as electrolyte and was used for the recognition of DOPA enantiomers. The electrochemical parameters of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe used for the chiral recognition of DOPA enantiomers are

Table 2 Electrochemical parameters of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe films

Sample	Redox peak potentials				Redox stability ^a	
	10 mV·s ⁻¹		300 mV·s ⁻¹		100 th	1000 th
	E_{ox} (V)	E_{red} (V)	E_{ox} (V)	E_{red} (V)		
(D)-PProDOT-Boc-Phe	0.33	0.30	0.34	0.31	98.5%	97.6%
(L)-PProDOT-Boc-Phe	0.35	0.27	0.50	0.28	96.7%	96.5%

^a Scan rate: 150 mV·s⁻¹.

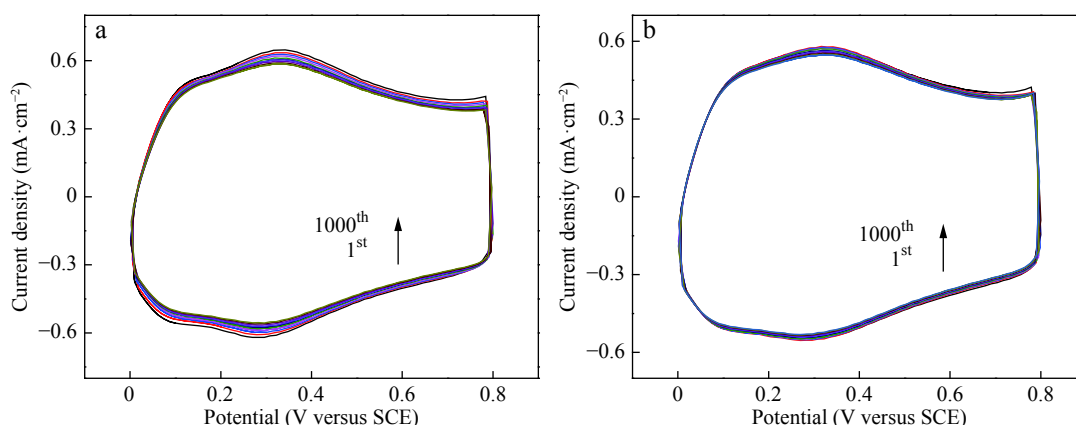


Fig. 8 CVs of (a) (D)-PProDOT-Boc-Phe and (b) (L)-PProDOT-Boc-Phe upon repeated cycling in monomer-free H₂SO₄ (0.25 mol·L⁻¹) at room temperature. Scan rate: 150 mV·s⁻¹

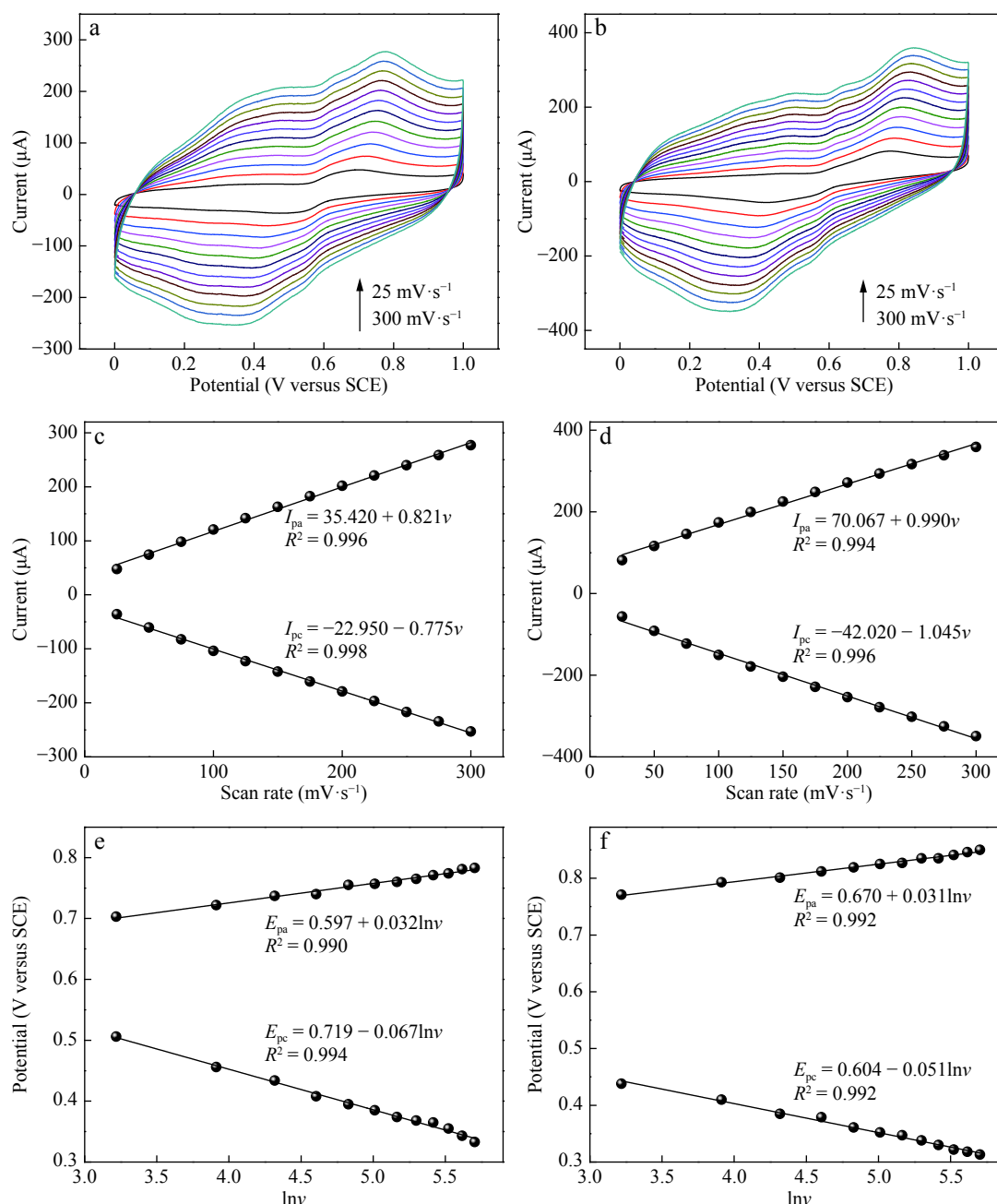


Fig. 9 Cyclic voltammogram of (a) (D)-PProDOT-Boc-Phe and (b) (L)-PProDOT-Boc-Phe in 0.25 mol·L⁻¹ H₂SO₄ containing 0.5 mmol·L⁻¹ DOPA (racemate) at different scan rates; Redox peak current of (c) (D)-PProDOT-Boc-Phe and (d) (L)-PProDOT-Boc-Phe versus potential scan rates; Anodic and cathodic peak potentials of (e) (D)-PProDOT-Boc-Phe and (f) (L)-PProDOT-Boc-Phe versus natural logarithm scan rates

Table 3 Electrochemical parameters of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe used for the chiral recognition of DOPA enantiomers

Sample	DOPA	CV		SWV		DPV
		Anodic peak (μA)	Cathodic peak (μA)	Forward scan (μA)	Reverse scan (μA)	Peak current (μA)
(D)-PProDOT-Boc-Phe	D-DOPA	76.79	-69.99	205.4	-226.7	81.32
	L-DOPA	97.05	-73.12	264.9	-301.7	150.1
(L)-PProDOT-Boc-Phe	D-DOPA	167.20	-158.6	647.3	-616.8	348.6
	L-DOPA	145.80	-135.5	551.8	-560.9	328.2

listed in Table 3. As shown in Figs. 10(a) and 10(b), D-DOPA and L-DOPA showed significant redox peaks at around 0.3 V with the PProDOT-Boc-Phe modified glassy

carbon electrode (PProDOT-Boc-Phe/GCE). That could be caused by the two-electron-two-proton oxidation and reduction of DOPA and dopaquinone. The SWV curves of

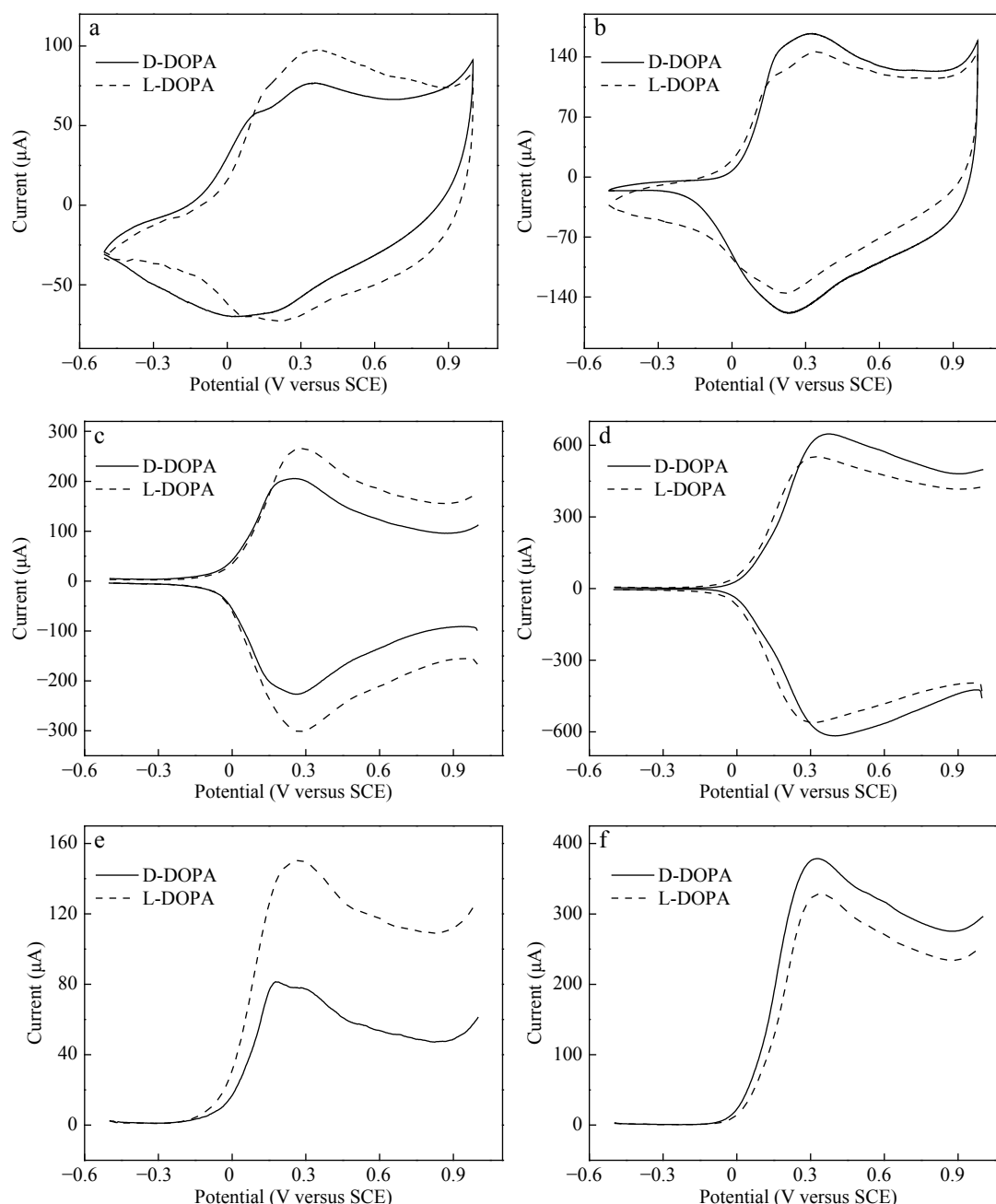


Fig. 10 (a, b) CVs, (c, d) SWVs, and (e, f) DPVs of (a, c, and e) (D)-PProDOT-Boc-Phe and (b, d, and f) (L)-PProDOT-Boc-Phe modified electrodes in 0.25 mol·L⁻¹ H₂SO₄ containing 0.5 mmol·L⁻¹ DOPA

DOPA are shown in Figs. 10(c) and 10(d), and different peak currents of D-DOPA and L-DOPA can also be seen. These phenomena indicated that (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe exhibited chiral recognition ability for DOPA in the SWV. The recognition efficiency can be estimated from the peak current ratio of enantiomers ($I_{\text{D-DOPA}}/I_{\text{L-DOPA}}$ or $I_{\text{L-DOPA}}/I_{\text{D-DOPA}}$). As shown in Figs. 10(c) and 10(d), the recognition efficiencies of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe using SWV were 1.28 and 1.17, respectively. According to our previous work,^[24] the recognition efficiency of PEDOT-Boc-Phe measured by SWV was 1.16. These results implied that chiral PProDOT-Boc-Phe had better chiral recognition ability than PEDOT-

Boc-Phe did for the recognition of DOPA. Monomer with single chiral center was propitious to enhance the stereoselective interactions of chiral conducting polymer-based electrochemical sensors and enantiomers. In addition, the current responses of DOPA enantiomers were studied by DPV, and obvious differences were obtained for (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe. As shown in Figs. 10(e) and 10(f), the recognition results of DPVs were consistent with the previous results from CVs and SWVs, which demonstrated that (D)-PProDOT-Boc-Phe had a higher response to L-DOPA, while (L)-PProDOT-Boc-Phe had a higher response to D-DOPA. The recognition efficiencies of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-

Phe measured by DPV were 1.85 and 1.06, respectively. These results demonstrated that chiral PProDOT-Boc-Phe had chiral recognition ability for the recognition of DOPA. Compared with spectroscopic and chromatographic methods, chiral PProDOT-Boc-Phe-based electrochemical sensors were rapid and simple, and required no complicated pretreatment for enantioselective recognition of DOPA enantiomers.^[6,7,9] In addition, with higher stereospecificity functional group, chiral PProDOT-Boc-Phe showed higher recognition efficiency than PEDOT-Boc-Phe did by using electrochemical methods.^[24] Moreover, the chiral PProDOT-Boc-Phe provided a potential for practical application in chiral discrimination.

CONCLUSIONS

In this study, a pair of amino-functionalized chiral EDOT derivatives, ProDOT-Boc-Phe, were synthesized. PProDOT-Boc-Phe modified glassy carbon electrode was utilized for the chiral recognition of DOPA enantiomers. The chiral PProDOT-Boc-Phe prepared *via* electrochemical polymerization showed good redox activity and stability. In addition, the chiral PProDOT-Boc-Phe modified electrodes could identify DOPA enantiomers rapidly and efficiently. (D)-PProDOT-Boc-Phe had a higher response to L-DOPA, while (L)-PProDOT-Boc-Phe had a higher response to D-DOPA. The recognition efficiency of (D)-PProDOT-Boc-Phe and (L)-PProDOT-Boc-Phe using SWV were 1.28 and 1.17, respectively. The results indicated that, for chiral conducting polymers, avoiding extra chiral center and increasing steric hindrance of chiral center are important to realize chiral recognition.

ACKNOWLEDGMENTS

The authors are grateful to the National Natural Science Foundation of China (Nos. 51762020 and 51603095), the Natural Science Foundation of Jiangxi Province (Nos. 20171ACB20026 and 20181BAB206015), the Jiangxi Provincial Department of Education (No. GJJ170662), the Innovation Driven "5511" the Natural Science Foundation of Jiangxi Province (No. 20165BCB18016), Students Innovation and Entrepreneurship Training Program (No. 20181204066), Projects for Postgraduate Innovation in Jiangxi (No. YC2017-X19), and the Jiangxi Provincial Key Laboratory of Drug Design and Evaluation (No. 20171BCD40015) for their financial support of this work.

REFERENCES

- Sanganyado, E.; Lu, Z. J.; Fu, Q. G.; Schlenk, D.; Gan, J. Chiral pharmaceuticals: A review on their environmental occurrence and fate processes. *Water Res.* **2017**, *124*, 527–542.
- Ribeiro, C.; Santos, C.; Gonçalves, V.; Ramos, A.; Afonso, C.; Tiritan, M. E. Chiral drug analysis in forensic chemistry: An overview. *Molecules* **2018**, *23*, 262–309.
- Pezzoli, G.; Zini, M. Levodopa in Parkinson's disease: From the past to the future. *Expert Opin. Pharmacol.* **2010**, *11*, 627–635.
- Poewe, W.; Antonini, A.; Zijlmans, J. C.; Burkhard, P. R.; Vingerhoets, F. Levodopa in the treatment of Parkinson's disease: An old drug still going strong. *Clin. Interv. Aging* **2010**, *5*, 229–238.
- Zhang, Q.; Huang, Y.; Guo, L.; Chen, C.; Guo, D.; Chen, Y.; Fu, Y. DNA-based nanocomposite as electrochemical chiral sensing platform for the enantioselective interaction with quinine and quinidine. *New J. Chem.* **2014**, *38*, 4600–4606.
- Watarai, H.; Kurahashi, Y. Chiral recognition of 2-alkylalcohols with magnetic circular dichroism measurement of porphyrin J-aggregate on silica gel plate. *Anal. Chem.* **2016**, *88*, 4619–4623.
- Balint, A.; Cârje, A. G.; Muntean, D. L.; Imre, S. The influence of some parameters on chiral separation of ibuprofen by high-performance liquid chromatography and capillary electrophoresis. *Acta Med. Mar.* **2017**, *63*, 36–40.
- Lazzeretti, P. Chiral discrimination in nuclear magnetic resonance spectroscopy. *J. Phys.: Condens. Matter* **2017**, *29*, 443001–443094.
- Schurig, V. Chiral separations using gas chromatography. *TrAC, Trends Anal. Chem.* **2002**, *21*, 647–661.
- Prior, A.; Coliva, G.; Jong, G. J.; Somsen, G. W. Chiral capillary electrophoresis with UV-excited fluorescence detection for the enantioselective analysis of 9-fluorenylmethoxycarbonyl-derivatized amino acids. *Anal. Bioanal. Chem.* **2018**, *410*, 4979–4990.
- Huang, Y.; Han, Q.; Zhang, Q.; Guo, L.; Guo, D.; Fu, Y. A fast chiral sensing to DOPA enantiomers *via* poly-lysine films matrices. *Electrochim. Acta* **2013**, *113*, 564–569.
- Trojanowicz, M. Enantioselective electrochemical sensors and biosensors: A mini-review. *Electrochem. Commun.* **2014**, *38*, 47–52.
- Wang, Z.; Xu, J.; Yao, Y.; Zhang, L.; Wen, Y.; Song, H.; Zhu, D. Facile preparation of highly water-stable and flexible PEDOT:PSS organic/inorganic composite materials and their application in electrochemical sensors. *Sens. Actuators, B* **2014**, *196*, 357–369.
- Manoli, K.; Magliulo, M.; Torsi, L. Chiral sensor devices for differentiation of enantiomers. *Topics Curr. Chem.* **2013**, *341*, 133–176.
- Li, J.; Hu, X.; Wang, J. Electrochemical recognition of chiral molecules with poly(4-bromoaniline) modified gold electrode. *Electroanalysis* **2013**, *25*, 1975–1980.
- Zhang, Y.; Lu, B.; Dong, L.; Sun, H.; Hu, D.; Xing, H.; Duan, X.; Chen, S.; Xu, J. Solvent effects on the synthesis, characterization and electrochromic properties of acetic acid modified polyterthiophene. *Electrochim. Acta* **2016**, *220*, 122–129.
- Caras-Quintero, D.; Bäuerle, P. Synthesis of the first enantiomerically pure and chiral, disubstituted 3,4-ethylenedioxythiophenes (EDOTs) and corresponding stereo- and regioregular PEDOTs. *Chem. Commun.* **2004**, 926–927.
- Jeong, Y. S.; Akagi, K. Control of chirality and electrochromism in copolymer-type chiral PEDOT derivatives by means of electrochemical oxidation and reduction. *Macromolecules* **2011**, *44*, 2418–2426.
- Dong, L.; Zhang, Y.; Duan, X.; Zhu, X.; Sun, H.; Xu, J. Chiral PEDOT-based enantioselective electrode modification material for chiral electrochemical sensing: Mechanism and model of chiral recognition. *Anal. Chem.* **2017**, *89*, 9695–9702.
- Dong, L.; Zhang, L.; Duan, X.; Mo, D.; Xu, J.; Zhu, X. Synthesis and characterization of chiral PEDOT enantiomers bearing chiral moieties in side chains: Chiral recognition and its mechanism using electrochemical sensing technology. *RSC Adv.* **2016**, *6*, 11536–11545.
- Dong, L.; Lu, B.; Duan, X.; Xu, J.; Hu, D.; Zhang, K.; Sun, H.; Ming, S.; Wang, Z.; Zhen, S. Novel chiral PEDOTs for selective recognition of 3,4-dihydroxyphenylalanine enantiomers:

- Synthesis and characterization. *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53*, 2238–2251.
- 22 Dong, L. Q.; Hu, D. F.; Duan, X. M.; Wang, Z. P.; Zhang, K. X.; Zhu, X. F.; Sun, H.; Zhang, Y. S.; Xu, J. K. Synthesis and characterization of D-/L-methionine grafted PEDOTs for selective recognition of 3,4-dihydroxyphenylalanine enantiomers. *Chinese J. Polym. Sci.* **2016**, *34*, 563–577.
 - 23 Hu, D.; Lu, B.; Duan, X.; Xu, J.; Zhang, L.; Zhang, K.; Zhang, S.; Zhen, S. Synthesis of novel chiral L-leucine grafted PEDOT derivatives with excellent electrochromic performances. *RSC Adv.* **2014**, *4*, 35597–35608.
 - 24 Hu, D.; Lu, B.; Zhang, K.; Sun, X.; Xu, J.; Duan, X.; Dong, L.; Sun, H.; Zhu, X.; Zhen, S. Synthesis of novel chiral L-phenylalanine grafted PEDOT derivatives with electrochemical chiral sensor for 3,4-dihydroxyphenylalanine discrimination. *Int. J. Electrochem. Sci.* **2015**, *10*, 3065–3081.
 - 25 Zong, K.; Madrigal, L.; Groenendaal, L. B.; Reynolds, J. R. 3,4-Alkylenedioxy ring formation via double Mitsunobu reactions: An efficient route for the synthesis of 3,4-ethylenedioxythiophene (EDOT) and 3,4-propylenedioxythiophene (ProDOT) derivatives as monomers for electron-rich conducting polymers. *Chem. Commun.* **2002**, 2498–2499.
 - 26 Kumar, A.; Kumar, A. Single step reductive polymerization of functional 3,4-propylenedioxythiophenes via direct C–H arylation catalyzed by palladium acetate. *Polym. Chem.* **2010**, *1*, 286–288.
 - 27 Lu, B.; Lu, Y.; Wen, Y.; Duan, X.; Xu, J.; Chen, S.; Zhang, L. Synthesis, characterization, and vitamin C detection of a novel L-Alanine-modified PEDOT with enhanced chirality. *Int. J. Electrochem. Sci.* **2013**, *8*, 2826–2841.
 - 28 Niu, J.; Chen, S.; Zhang, W.; Zhang, W.; Chai, K.; Ye, G.; Li, D.; Zhou, W.; Duan, X.; Xu, J. Supercapacitor properties of nanowire poly((3,4-dihydro-2H-thieno[3,4-b][1,4] dioxepin-3-yl)methanol) free-supporting films. *Electrochim. Acta* **2018**, *283*, 488–496.
 - 29 Lu, B.; Zhang, S.; Qin, L.; Chen, S.; Zhen, S.; Xu, J. Electro-synthesis of poly(3,4-ethylenedithiathiophene) in an ionic liquid and its electrochemistry and electrochromic properties. *Electrochim. Acta* **2013**, *106*, 201–208.
 - 30 Lu, Y.; Wen, Y. P.; Lu, B. Y.; Duan, X. M.; Xu, J. K.; Zhang, L.; Huang, Y. Electrosynthesis and characterization of poly(hydroxy-methylated-3,4-ethylenedioxythiophene) film in aqueous micellar solution and its biosensing application. *Chinese J. Polym. Sci.* **2012**, *30*, 824–836.
 - 31 Lu, B.; Zhen, S.; Zhang, S.; Xu, J.; Zhao, G. Highly stable hybrid selenophene-3,4-ethylenedioxythiophene as electrically conducting and electrochromic polymers. *Polym. Chem.* **2014**, *5*, 4896–4908.
 - 32 Anson, F. C. Application of potentiostatic current integration to the study of the adsorption of cobalt(III)-(ethylenedinitrilo) tetraacetate on mercury electrodes. *Anal. Chem.* **1964**, *36*, 932–934.
 - 33 Yao, Y.; Zhang, L.; Wen, Y.; Wang, Z.; Zhang, H.; Hu, D.; Xu, J.; Duan, X. Voltammetric determination of catechin using single-walled carbon nanotubes/poly(hydroxymethylated-3,4-ethylenedioxythiophene) composite modified electrode. *Ionics* **2015**, *21*, 2927–2936.
 - 34 Laviron, E. Adsorption, autoinhibition and autocatalysis in polarography and in linear potential sweep voltammetry. *J. Electroanal. Chem.* **1974**, *52*, 355–393.
 - 35 Velasco, J. G. Determination of standard rate constants for electrochemical irreversible processes from linear sweep voltammograms. *Electroanalysis* **1997**, *9*, 880–882.
 - 36 Chen, L.; Chang, F.; Meng, L.; Li, M.; Zhu, Z. A novel electrochemical chiral sensor for 3,4-dihydroxyphenylalanine based on the combination of single-walled carbon nanotubes, sulfuric acid and square wave voltammetry. *Analyst* **2014**, *139*, 2243–2248.