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A chiral electrochemical sensor for propranolol based on multi-walled carbon nanotubes/ionic liquids nanocomposite

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ABSTRACT

A novel chiral electrochemical sensor based on multi-walled carbon nanotubes (MWCNTs)/ionic liquids (ILs) nanocomposite was developed and applied to the enantiomeric recognition of propranolol (PRO). Mechanisms for chiral sensing were discussed in terms of the formation of an efficient chiral nanospace originating from the weak interactions between quasi-chiral MWCNTs and versatile ILs. This work provided new evidence that the electro-oxidation of PRO should result from its hydroxyl group. Herein the ratio of oxidation peak currents, instead of the commonest shift of peak potential, was used to sense the enantiomeric fraction (EF) of (*R*)-PRO with a linear correlation coefficient of 0.9936. This simple and reliable sensor was successfully applied in an accurate determination of the enantiomeric purity of reagent, as well as the evaluation of waste water treatment efficiency.

1. Introduction

Propranolol (1-isopropylamino-3-(1-naphthyloxy)-2-propranolol) is a widely used β-adrenergic blocking agent for the treatment of hypertension, cardiac arrhythmia and angina pectoris. It possesses one chiral center and an inherent high degree of enantioselectivity in binding to the β-adrenergic receptor [1]. Basically, its enantiomers have markedly different pharmacodynamics and pharmacokinetics in some cases. For example, the metabolism and elimination of (*S*)-PRO is faster than (*R*)-PRO, and thus the (*S*)-PRO is approximately 100 times more potent than (*R*)-PRO [2,3]. Moreover, for chiral compounds that undergo enantioselective biodegradation, the EF of a compound would reveal information about its history [4]. It was recently demonstrated that the determination of EF value of PRO may be useful in detecting and documenting contaminants related to leaking sewers and combined sewer overflows. During successive sewage treatment steps, the EF value of (*R*)-PRO in racemate would decrease to even less than 40% regardless the concentration of PRO [5]. Consequently, the therapeutical and environmental relevance of PRO justifies a great interest in developing an accurate analytical procedure to assess the enantiomeric composition of the PRO.

Several methods for the enantioseparation and determination of PRO have been reported in the past years, by high-performance liquid chromatography [6,7], capillary electrophoresis [8,9], nuclear magnetic resonance spectroscopy [10,11] and molecular fluorescence [12,13]. To our knowledge, there is no study available on the utilization of electrochemical method for chiral sensing of PRO. Actually, compared with the above methods, electrochemical sensors are an excellent choice because they can provide low cost, high speed, real time and on-line operation. But due to some inherent problems such as the less processes of separation on the electrode surface, it has always been a very serious challenge to design an effective chiral electrochemical sensor [14–16].

As far as the fabrication of electrochemical sensor is concerned, nothing is more important than the selection of sensing interface. In recent years, a so-called Bucky gel has been receiving increasing attention for application in the electrochemical determination of some biomolecules such as dopamine, uric acid and glucose and so on, especially by our group [17–21]. Not like ordinary organogels or hydrogels, this gel discovered by Fukushima in 2003 [22] is a kind of mixture of MWCNTs and ILs, which combines the advantages of these two materials. Basically, the most remarkable characteristic for ILs is that they can be designed by choosing specific cations and anions to meet specific requirements. In addition, it has been found that the chiral angles of MWCNTs grown by chemical vapor deposition (CVD) method could be observed [23,24]. So the motivation for this study is derived primarily from the anticipation of the development of a chiral sensor for electroactive PRO, by combining quasi-chiral MWCNTs with versatile ILs. The quantitative assay of the *R*/*S* ratio in enantiomeric mixtures may be achieved by using MWCNTs/ILs nanocomposite with quasi-chiral centers.

2. Experimental

2.1. Materials

Racemic and enantiomerically pure propranolol hydrochlorides (99%) were purchased from Sigma Aldrich. The MWCNTs

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with mean diameter of about 30 nm were obtained from the Tsinghua University of China as gifts. They were produced by CVD method, and the procedures of synthesis were reported elsewhere [25,26]. The ionic liquid of 1-octyl-3-methyl-imidazolium hexafluorophosphate ([Omim]PF_6) was synthesized according to the references [27,28]. The purities of MWCNTs and ILs are both more than 99%. Triply distilled water was used throughout the experiments. Highly pure nitrogen gas was used for deaeration. All other chemicals were of analytical reagent grade and used without further purification. Lake water was taken from Weiming Lake of Peking University.

2.2. Instrumentation

Electrochemical measurements were performed with a CHI 660C electrochemical workstation (Shanghai, China). The three-electrode electrochemical cell contains a glassy carbon electrode (GCE) or GCE modified with MWCNTs or ILs or MWCNTs/ILs nanocomposite, a platinum wire as counter electrode and a saturated calomel reference electrode (SCE).

2.3. Procedure

Based on our previous method [17], 20 mg [Omim]PF_6 mixing with 2.0 mg MWCNTs was sonicated in 2 ml dimethyl formamide (DMF) for 10 min, then the nanocomposite solution could be obtained. Prior to use, a GCE with a diameter of 3 mm was polished with 0.1 μm and 0.05 μm alumina slurry, and then washed ultrasonically in distilled water and ethanol for 2 min, respectively. After that, the chiral sensor was fabricated by casting 4.0 μl of the nanocomposite solution on the well-polished GCE and being dried under an infrared lamp. For comparative investigation, different amounts of [Omim]PF_6 and MWCNTs were mixed based on similar method as well.

To simulate sewage treatment, the PRO–spiked lake water was treated by boiling sterilization, UV disinfection and sitting for one week, respectively. The solution of racemic PRO and the spiked lake water were detected with the as-fabricated sensor. Before electrochemical measurements, all solutions were deaerated with highly pure nitrogen gas for 10 min and nitrogen was passed over the top of the solution during the experiments. In order to decrease experimental errors to the maximum, all voltammograms regarding PRO were recorded with the correction of corresponding background current. All measurements were conducted at room temperature (25 ± 2 °C).

3. Results and discussion

3.1. Electrochemical characteristic of PRO

There is no consensus yet about which group the electrochemical response of PRO originates from. Bishop et al. [29] tended to be the hydroxyl group while Radi et al. [30] thought the secondary amine group was more likely to be oxidated. Anyway, it is a commonly held view that the electro-oxidation of PRO involves 2 protons and 2 electrons. In our experiment, the effect of the pH of the supporting electrolyte solution on the cyclic voltammetric response of PRO was firstly investigated. In Britton–Robinson buffers (pH 4–8), no reduction peak appears in the cyclic voltammogram (not shown) measured at the MWCNTs/ILs–GCE modified electrode, showing the irreversibility of the electrochemical reaction of PRO. Besides the shift of oxidation peaks toward negative direction, originally one oxidation peak is splitting into two peaks with increasing pH (Fig. 1). Finally, 0.2 M phosphate buffer solution (PBS, pH 6.9) was chosen as the optimal medium solution based on the following reasons. (i) Under neutral condition the as-fabricated sensor is the stablest; (ii) Recta-acid are stronger, the electro-oxidation of PRO occurs at more positive potentials resulting in more interferences; (iii) Leaning alkalinity are stronger, more disadvantageous to the detection of treated wastewater; (iv) Employing the ratio of oxidation peak currents is more accurate for chiral sensing compared to a bit shift of peak potential in this system. As shown in Fig. 2, with the increasing of potential scan rate, both of the oxidation peaks shift toward positive direction while their peak currents increase linearly with the scan rate in the range of 0.005–0.600 V s^{-1}. All of these are the typical characteristics of irreversible adsorption peak.

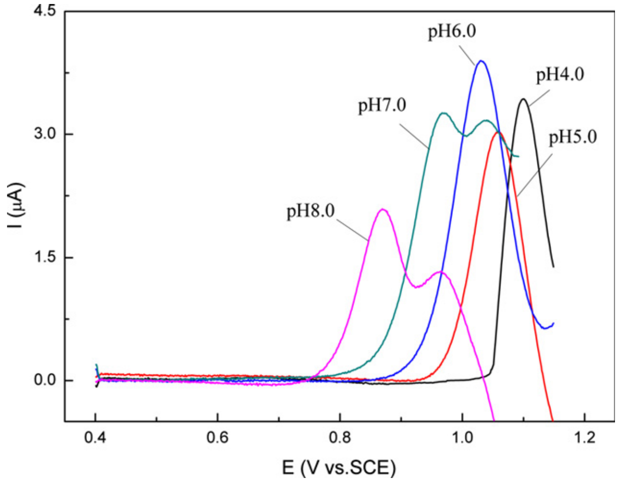


Fig. 1. The corrected voltammograms of 2.0 μM (*R,S*)-PRO at MWCNTs/ILs–GCE in B–R buffer at different pH values. Scan rate, 30 mV s^{-1}; open potential, 0.4 V; quiet time, 480 s.

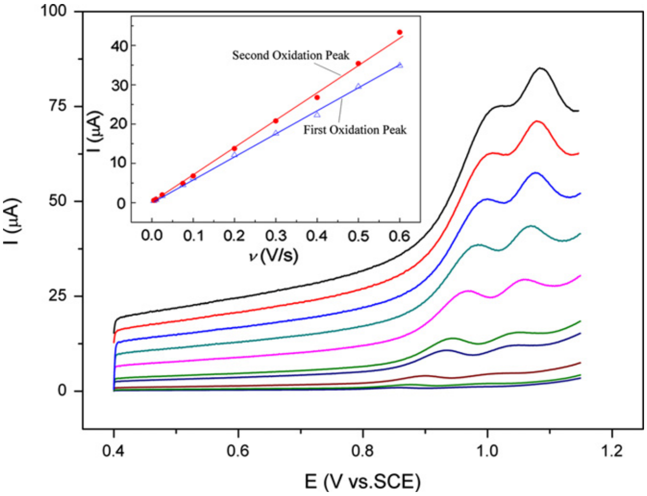


Fig. 2. The corrected voltammograms of 2.0 μM (*R,S*)-PRO at MWCNTs/ILs–GCE in 0.2 M PBS (pH 6.9) at different potential scan rates. Scan rate (V s^{-1}, from the bottom to the top), 0.005, 0.01, 0.025, 0.075, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6. Inset: Linear dependence of the first and the second oxidation peak currents on scan rate. Other conditions as in Fig. 1.

3.2. Chiral recognition of PRO

The constructing of a chiral environment is of critical importance for a chiral electrochemical sensor. Fig. 3 compares the electrochemical responses of PRO enantiomers at different electrodes

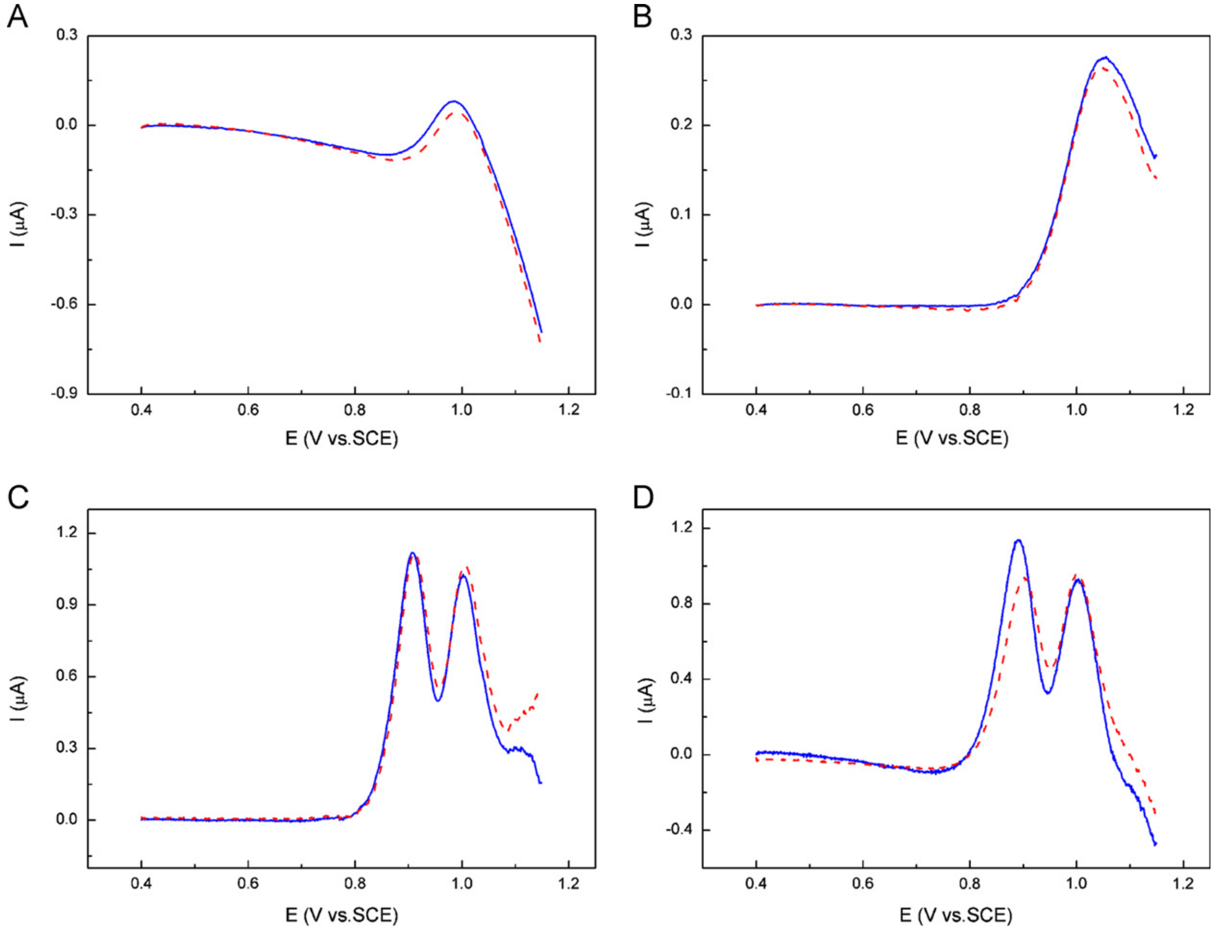
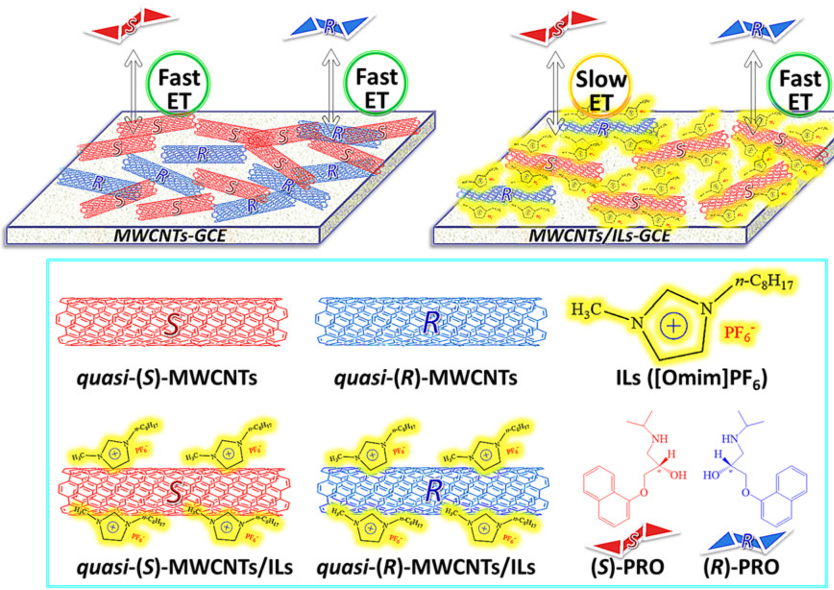


Fig. 3. The corrected voltammograms for 2.0 μM (*S*)-PRO (dash) or (*R*)-PRO (solid) at (A) GCE, (B) ILs–GCE, (C) MWCNTs-GCE, and (D) MWCNTs/ILs–GCE. Scan rate, 30 mV s^{-1}. Other conditions as in Fig. 2.

corresponding to naked GCE, ILs–GCE, MWCNTs-GCE and MWCNTs/ILs–GCE, respectively. As shown in Fig. 3A and B, both of (*R*)- and (*S*)-PRO show almost the same electrochemical responses such as one oxidation peak, similar peak current and similar peak potential. Obviously, they cannot be distinguished in the absence of chiral centers on the electrode surface. The only difference between naked GCE and ILs–GCE is that the presence of good conductive ILs leads to a substantial increase of peak current of PRO. If MWCNTs with quasi-chirality is introduced into the electrode surface, the situation will change. As before, two oxidation peaks can be observed, showing that MWCNTs drastically affect the electro-oxidation of PRO. Unfortunately, even the so-called quasi-chiral MWCNTs would not be sufficient to recognize PRO enantiomers (Fig. 3C). Our previous studies have shown that the entangled MWCNTs cannot function very well in the field of electrochemical sensor [21]. We supposed that PRO should exchange electrons with electrode by passing through the MWCNTs layer on the electrode surface. Due to the entanglement of MWCNTs, the efficient chiral microenvironment cannot be formed in spite that there is no apparent shortage of quasi-chiral centers. So either (*R*)-or (*S*)-PRO would choose a favorable way to avoid enantioseparation illustrated in Scheme 1. However, things are different upon the addition of ILs into modified layer. As shown in Fig. 3D, the voltammetric behavior of (*R*)-PRO presents some trends as potential variation and current variation, in comparison with (*S*)-PRO. For the first oxidation peak, about 20 mV (from 0.904 V to 0.888 V) of negative shift of peak potential as well as the increasing of peak current imply that (*R*)-PRO is easier to pass through the MWCNTs–ILs nanocomposite to lose the first electron on the GCE surface and thus show a fast electron transfer (ET), while (*S*)-PRO tends to be remained there to show a relatively slow ET. As to the second oxidation peak, it keeps almost the same peak potential together with a little enhanced peak current. Here, it will be not enough to assay the R/S ratio in enantiomeric mixtures just from a little change either in the potential or the current. Fortunately, we found a positive correlation between the EF value of (*R*)-PRO and the ratio of the above oxidation peak currents, based on the fact that the first oxidation peak is related to the chirality of PRO while the second is irrelevant. The current ratios are 1.37 and 0.98 corresponding to (*R*)- and (*S*)-PRO enantiomer, respectively. The ratio of (*R*)-PRO is about 40% higher than (*S*)-PRO, which may be sufficient to assess the enantiomeric composition of the PRO. On the other hand, this study simply proves that the electro-oxidation of PRO should originate from its hydroxyl group close to chiral carbon atom.

Various studies have been made to elucidate the weak interactions between MWCNTs and ILs, which essentially include H-bonding, π–π stacking, Van der Waals forces, and electrostatic forces and so on. Our previous results show that there are some kinds of non-covalent (π–π) interactions between MWCNTs side wall and the imidazole loop of ILs [18–21]. Golovanov et al. [31] ever reported an unexpectedly high melting point (210 °C) of 1-methyl-3-propyl-imidazolium SiF_6 IL, resulting from the presence of extremely short $C–H\cdots F$ contacts in the crystal. In our case of MWCNTs/ILs nanocomposite, we suppose that such a short $C–H\cdots F$ contact would be further enhanced with the aid of high electric charge density inside MWCNTs, leading to the formation of a multiple stable hydrogen bond networks. These charge-assisted hydrogen bonds together with π–π interaction



Scheme 1. Schematic illustration of the MWCNTs/ILs nanocomposite based sensor for distinguishing chiral PRO.

Table 1
Results for the EF values of water sample with different treatment modes.

Treatment Mode	I_{p1}/I_{p2}	EF
Without treatment	1.14	47.1%
Boiling sterilization	1.07	27.9%
UV disinfection	1.07	26.1%
Sitting for one week	1.07	28.6%

bring about the shortening of the intermolecular spacing. At this point, an efficient chiral nanospace would be formed, which biases towards the *S* type in this system. So the (*R*)-PRO is easier to pass through the nanocomposite while the (*S*)-PRO is hindered, as illustrated in Scheme 1. The enantioseparation in this interface is so fast that only a statistical electrochemical behavior can be observed. Anyway, it is possible to determine the EF value by one variable peak current and another relatively constant peak current, even with no need to know the accurate amount of PRO.

3.3. *Optimization of the sensing conditions*

In this system, although the quasi-chiral MWCNTs play a key role to recognize the chiral PRO, they would not function without ILs. With proper mixed ratio of ILs to MWCNTs, better recognition effect could be obtained because the MWCNTs were pulled away from the entanglement by interacting with ILs, so that more chiral centers could be exposed. However, the effect would turn worse if there was too much ILs in the nanocomposite. That is because all the MWCNTs were wrapped up by the ILs, and the advantage of MWCNTs was counteracted. The optimal mixing ratio of ILs to MWCNTs is 10:1. Likewise, the amount of nanocomposite on GCE is double-edged. Theoretically, more nanocomposites favor the recognition effect. But their side effects are both the decrease of electrochemical response and sensor stability. 4 μl was chosen as the optimal. Other parameters including quiet time and scan rate and so on have also been optimized.

3.4. *Analysis and application*

With the total concentration of PRO being kept as 0.2 μM, a series of voltammograms corresponding different EF value of (*R*)-PRO in enantiomers mixture were obtained under the optimal experimental conditions (Fig. 4). The oxidation currents ratio reveals a linear dependence for EF value with the correlation coefficient of 0.9936 (Inset in Fig. 4). The EF value of a racemic PRO reagent was determined to be 51.2% by the oxidation current ratio of 1.16, which was consistent with the listed value. The spiked lake water was detected after being treated by three kinds of methods, and the results are shown in Table 1. So the as-fabricated sensor can be used to evaluate sewage treatment effect in the environment field.

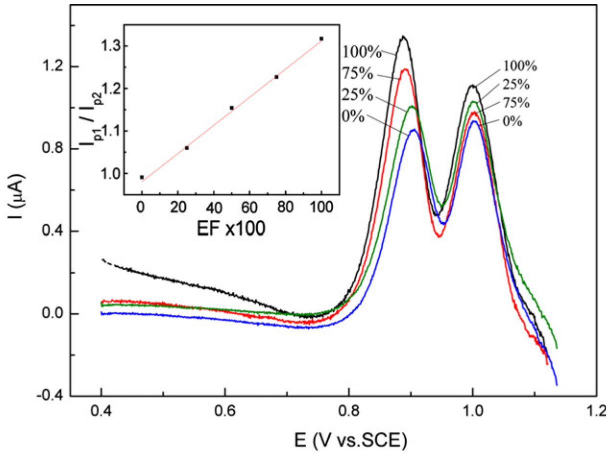


Fig. 4. The corrected voltammograms for different EF values of (*R*)-PRO. Inset: Linear relationship between EF of (*R*)-PRO and the oxidation currents ratio. Other conditions as in Fig. 3D.

4. Conclusions

In summary, an electrochemical sensor for chiral PRO was developed based on MWCNTs/ILs nanocomposite without other chiral selectors. The features of this new approach are simplicity, rapidity and sensitivity. Its application to rapid detection of EF values matches the therapeutical and environmental needs.

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