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A novel sensor made of Antimony Doped Tin Oxide-silica composite sol on a glassy carbon electrode modified by single-walled carbon nanotubes for detection of norepinephrine

Zhao Wang, Kai Wang, Lu Zhao, Shigan Chai, Jinzhi Zhang *, Xiuhua Zhang, Qichao Zou *

Hubei Collaborative Innovation Center for Advanced Organic Chemical Materials, College of Chemistry and Chemical Engineering, Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University, Wuhan 430062, China

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ABSTRACT

In this study, we designed a novel molecularly imprinted polymer (MIP), Antimony Doped Tin Oxide (ATO)-silica composite sol, which was made using a sol–gel method. Then a sensitive and selective imprinted electrochemical sensor was constructed with the ATO-silica composite sol on a glassy carbon electrode modified by single-walled carbon nanotubes (SWNTs). The introduction of SWNTs increased the sensitivity of the MIP sensor. The surface morphology of the MIP and MIP/SWNTs were characterized by scanning electron microscopy (SEM), and the optimal conditions for detection were determined. The oxidative peak current increased linearly with the concentration of norepinephrine in the range of 9.99×10^{-8} M to 1.50×10^{-5} M, as detected by cyclic voltammetry (CV), the detection limit was 3.33×10^{-8} M (S/N = 3). In addition, the proposed electrochemical sensors were successfully applied to detect the norepinephrine concentration in human blood serum samples. The recoveries of the sensors varied from 99.67% to 104.17%, indicating that the sensor has potential for the determination of norepinephrine in clinical tests. Moreover, the imprinted electrochemical sensor was used to selectively detect norepinephrine. The analytical application was conducted successfully and yielded accurate and precise results.

1. Introduction

Norepinephrine (NEP) is a catecholamine neurotransmitter in the brain, and it has the important physiological effects as a neurotransmitter and hormone in the circulatory system. Consequently, determination of its content in human blood or urine can be used to diagnose some diseases [1–2], which is of vital significance. At present, various methods have been established to determine the concentration of norepinephrine in human blood or urine, including chromatography (HPLC) [3], capillary electrophoresis (CE), thin-layer chromatography (TLC) [4–5], spectrophotometry, fluorescence spectrometry [6–8] and electrochemical biosensors [9]. Although some of the methods have high sensitivity and specificity, complicated and expensive instruments are required. Consequently, electrochemical sensors are becoming important tools in medical, biological and environmental analysis due to their simplicity, high sensitivity and relative cheapness. Furthermore, the sensitivity and specificity of these electrochemical sensors, such as molecularly imprinted polymers (MIPs) sensors, can be considerably improved by the design and development of new materials. Various biosensors for NEP detection were prepared by researchers with different methods [10–18]. We propose the method of molecular imprinting to obtain a lower detection limit of norepinephrine.

Molecular imprinting is a well-established and easy technique for synthesizing MIPs with specific molecular recognition capacity. The imprinting process involves polymerizing functionalized monomers in the presence of the template molecule. Upon removal of the template molecule, molecular holes remain and are specific in shape and size to the target molecule. As a rule, the method of molecular imprinting involves the polymerization of a functional monomer and a cross-linker around a template molecule. In the first step, functional monomers are assembled around the template molecule by covalent bonds. Following this preassembly step, the monomer-template complex is polymerized with the cross-linker and initiator in a porogenic solvent. After polymerization is complete, the template molecule is removed from the MIP by washing with an organic solvent and specific binding sites for the template are prepared in MIP. Then, the stoichiometric relation between the functional monomer and template molecule is confirmed. The specific molecular recognition sites are evenly dispersed. However, the covalent bonds are relatively strong. Therefore, more energy is required when the covalent bonds are formed or fractured, and the process of combination and separation of the template molecule and functional monomer cannot be completed in a short time, which is disadvantageous to many types of detection that must be performed rapidly. However, if the non-covalent bonds are adopted, the template molecule and

* Corresponding authors.
E-mail address: qichaozou58@126.com (Q. Zou).

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functional monomer can effect mutually or separate rapidly. In solution, the template molecule and functional monomer can mutually effect with the non-covalent bonds, such as hydrogen bonds and electrostatic interactions. Consequently, many functional monomers, which have structures containing hydrogen bonds, are used to compound molecular imprinted polymers. Various types of siloxane [19–22] have been applied for this purpose.

Recently, there has been considerable interest in antimony tin oxide (ATO) nanostructured materials as a film-forming material because they have optical transparency and relatively good conductivity [23–33]. However, ATO modified electrodes have not been researched. Furthermore, silica sol–gel, as an inorganic material with advantages such as structural rigidity and high surface area, has been used for the prospective 3D inorganic matrices in many cases. The combination of two or three types of monomers can lead to a molecular imprinted polymer that has better recognition ability. However, there are scarce reports on the design of hybrid ATO-silica sol–gel materials.

The aim of this paper is to construct a highly sensitive and selective electrochemical sensor. We designed ATO-silica sol–gel materials with structural rigidity and a high surface area of silica sol–gel, as well as relatively good conductivity. Because carbon nanotubes (CNTs) have desirable properties, such as good electrocatalytic activity, high surface area, and excellent electrical conductivity [34–39], we used CNTs to modify electrodes to promote the transfer of biological molecules and electrons from the electrodes [40–42], increase the electrochemical signals [43–45] and improve the sensitivity of the sensors [46–49]. After the ATO-silica composite sol was obtained, we fixed the template molecule, norepinephrine, in the composite sol to obtain the MIP solution. The MIP-modified glassy carbon electrode was acquired by dropping the MIP solution onto the surface of a glassy carbon electrode that had been modified by CNTs. After washing the template molecule, norepinephrine, we used the electrochemical MIP-sensor to detect the existence of norepinephrine. Then, efficient and fast adsorption of template molecules was achieved when template molecules entered the imprinted sites through the aperture in the film because the ATO-silica composite film improved the electron transfer rate between norepinephrine and the electrode surface. This work offers a facile and efficient method to prepare ATO-silica composite film for electrochemical sensors application.

2. Experimental procedures

2.1. Apparatus

The electrochemical measurements were performed using a model CHI660C electrochemical workstation (CH Instruments, Chenhua, Shanghai, China) controlled by a personal computer. A three-electrode system was used in the measurements, with a molecularly imprinted modified glassy carbon electrode (3 mm in diameter) as the working electrode, a saturated calomel electrode (SCE) as the reference electrode and a platinum wire as the auxiliary electrode. The surface morphology of the films of different sols was measured using SEM (JSM6510LV, JEOL).

2.2. Reagents

Norepinephrine, epinephrine and dopamine hydrochloride were purchased from the Institute of Biological Products (China). Single-walled carbon nanotubes (SWNTs) were obtained from the Institute of Organic Chemistry (Chengdu, China). Silica sol was purchased from The League Chemical Co., Ltd. (Jiangyin, China). Tin antimony sol (ATO) was purchased from the Nano Technology Co., Ltd. (Shanghai, China). Anhydrous ethanol, glucose, ascorbic acid, hydrochloric acid (HCl) and sodium hydroxide (NaOH) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All reagents were of analytical reagent grade unless otherwise stated. Aqueous solutions were prepared using ultra-pure water (18.25 MΩ cm^{-1}) from an Aquapro Ultra-pure water system (Chongqin, China). Phosphate buffer solution (PBS) was prepared with 0.10 M Na_2HPO_4 and 0.10 M NaH_2PO_4 at pH 7.0.

2.3. Synthesis of ATO-silica composite sol

ATO-silica composite sol was prepared by combining silica sol and ATO sol at a ratio of 1:1, and diluting the silica sol and ATO sol with ultra-pure water and anhydrous ethanol, respectively to reach a the total solid content of 1%. The mixture was added to a flask and stirred for 4 h at room temperature. After agitation, a dark blue transparent composite sol was obtained.

Following the above process, a series of ATO-silica sols were prepared with different ratios of ATO and silica sol, including 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4 and 1:5. In addition, a series of different solid contents (0.1%, 0.5%, 1%, 3% and 5%) of ATO-silica composite sols were prepared. The ATO-silica sols were synthesized in 250-mL volumetric flasks.

2.4. Preparation of the MIPs and MIPs electrochemical sensor

A 0.5 mg/mL suspension of black SWNTs suspension was prepared by ultrasonic dispersion of purified SWNTs for 40 min with 5 mM sodium dodecylsulfate aqueous solution. The SWNTs/GCEs were acquired by dropping the SWNTs solution onto the surface of a glassy carbon electrode and drying for 6 h at room temperature.

First, we mixed ATO-silica sols with different solid contents and 10 mM norepinephrine. After stirring for 4 h at 30 °C, the homogeneous and transparent MIPs were obtained. Then, a bare glassy carbon electrode was treated and cleaned and the MIP-modified SWNTs/GCE was acquired by dropping the MIP solution on the surface of the SWNTs/GCE and drying for 10 h at room temperature. After washing off the norepinephrine, we used the electrochemical MIP-sensor to detect the existence of norepinephrine again.

2.5. Electrochemical measurements

The electrochemical measurements were conducted in 5.0 mL of PBS at pH 7.0. Cyclic voltammetry (CV) was performed from −0.2 V to 0.8 V, the scanning speed was 0.1 V/S, the scanning section number was 2 and the sampling interval was 0.001 V. The incubation solution was 5.0 mL of PBS with 5.0 μL of 10.0 mM norepinephrine.

3. Results and discussion

3.1. Surface morphology characterization by SEM analysis

SEM was employed to investigate the surface morphologies of the ATO film, ATO-silica composite film, silica film, SWNTs, ATO-silica/NEP and ATO-silica/NEP/SWNTs. As shown in Fig. 1A (ATO), the visible ATO nanoparticles were compactly and uniformly distributed on the surface. The silica sol particles (Fig. 1C) and the composite particles (Fig. 1B) were aggregated partially. It was found that a smooth and homogeneous film was covered onto the surface from Fig. 1E (ATO-silica/NEP) and Fig. 1F (ATO-silica/NEP/SWNTs), which is beneficial to mass transfer. However, the surface of the ATO-silica/NEP/SWNTs was rougher than the surface of the ATO-silica/NEP, which is due to the introduction of SWNTs (Fig. 1D) with tubular structure, the improvement of surface roughness can increase the binging sites of the template molecules.

3.2. Stoichiometric relationship between the template molecules and the functional monomer molecules

The proportion of the functional monomer and the template molecule (M/T) has a significant influence on the quantity and quality of the recognition sites of molecularly imprinted polymers. If the M/T