Analytica Chimica Acta 970 (2017) 30–37

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Discriminative sensing of DOPA enantiomers by cyclodextrin anchored graphene nanohybrids

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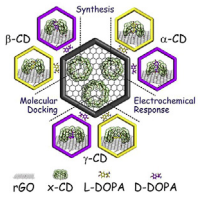
HIGHLIGHTS

- Discriminative sensing of DOPA enantiomers was investigated.
- Cyclodextrin (*x-CD/rGO*, *x*: α-, β-, γ-) anchored graphene nanohybrids were employed.
- The electrochemical measurements and molecular docking studies were performed.
- The results showed that γ-*CD/rGO* was the most convenient nanohybrid.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 8 November 2016
Received in revised form
8 January 2017
Accepted 30 March 2017
Available online 7 April 2017

Keywords:
Graphene nanohybrid
DOPA
Enantioselective sensor
Discrimination
Voltammetry

ABSTRACT

Discriminative sensing of chiral species with a convenient and robust system is a challenge in chemistry, pharmaceutics and particularly in biomedical science. Advanced nanohybrid materials for discrimination of these biologically active molecules can be developed by combination of individual obvious advantages of different molecular scaffolds. Herein, we report on the comparison of the performance of cyclodextrin functionalized graphene derivatives (*x-CD/rGO*, *x*: α-, β-, γ-) for discrimination of DOPA enantiomers. Within this respect, electrochemical measurements were conducted and the experimental results were compared to molecular docking method. Thanks to cavity size of γ-*CD* and the unique properties of graphene, *rGO*/γ-*CD* nanohybrid is capable of selective recognition of DOPA enantiomers. Limit of detection (LOD) value and sensitivity were determined as 15.9 μM and 0.2525 μA μM^{-1} for *D*-DOPA, and 14.9 μM and 0.6894 μA μM^{-1} for *L*-DOPA.

1. Introduction

Enantiomeric purity of chiral species, which plays an essential role particularly in chemical and biomedical systems, is considered as the major point for the benefit of maximized efficacy and minimized side effects in the drug discovery and development processes [1,2]. Enantiomers, two antipodes of a pair of mirror image, possess identical physico-chemical properties. However, one enantiomer of a chiral drug may often influence therapeutic effects whereas the use of other may entail the risk of serious detrimental effects [3]. For instance, 3,4-dihydroxy-*L*-phenylalanine (*L*-DOPA), also known as levodopa produced by several gram-negative bacteria, is an important therapeutic agent used for many neurodegenerative diseases, particularly for Parkinson. It is also used as the precursor to synthesis of dopamine, which is an

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http://dx.doi.org/10.1016/j.aca.2017.03.052
0003-2670/

important drug used in the treatment of acute circulation disorders. On the contrary, 3,4-dihydroxy-*D*-phenylalanine (*D*-DOPA) is inactive and has toxic effect on living systems [4].

Considering the mentioned crucial role of chirality, the development of convenient techniques for analysis of the enantiomeric purity of substances has received much attention in recent years. Generally, enantiomers are detected through highly sensitive and robust techniques such as high-performance liquid chromatography by employing chiral column chromatography and circular dichroism [5]. Rather than use of these current methodologies which require high cost of instrumentation, trained person and long experimental procedures, chiral detection by combination of advanced detection devices with rather simple chiral recognition in solution has much higher potential in practical use. In this respect, electrochemical sensing at a modified electrode surface is one of the promising methods [6].

Enantioselectivity is the major challenge encountered in developing a sensing mode for discriminative sensing of chiral substances [7]. Particularly due to this challenge, the development of advanced materials capable of discrimination of enantiomers with a convenient analysis mode is under active research in biosensing and nanotechnology. Unification of the superior characteristics of two different substances may create an advanced matrix to develop a sensing approach. Within this framework, due to its extraordinary and fascinating properties, graphene is definitely the most studied 2D nanomaterial. Graphene is used as a surface for anchoring an enantioselective unit onto its surface to build molecular scaffolds with unique and widely varying properties [8]. As an enantioselective unit, cyclodextrin (CD) has become of considerable interest in chemistry and pharmaceutical industry owing to its ability to increase the solubility of drugs, being stable at low pH (down to 3) and high temperature (below 200 °C) as well as its selectivity allowing to avoid interferences for discrimination of chiral molecules [9]. In this respect, combination of graphene with CD can be considered as an attractive solution in the sense of chiral enantiomers.

In this study, in consideration of the structural characteristics aforementioned above, a versatile and robust graphene-based chiral analysis system is developed for discriminative sensing of DOPA enantiomers. Previously, we have reported electrochemical discrimination of tryptophan [10,11], mandelic acid [12] and cystine [9] enantiomers by graphene-based modified electrodes. Differently from these studies, the current work represents the comparison of the performance of cyclodextrin functionalized graphene derivatives (*rGO/x-CD, x: α, β, γ*) for discrimination of DOPA enantiomers. In recent years, successful attempts with sophisticated approaches have been occasionally reported for sensing of DOPA enantiomers with discrepancy in current intensity while no differentiation in the redox potentials. In the present study, the difference in oxidation peak potentials of DOPA enantiomers was successfully investigated by cyclodextrin functionalized graphene nanohybrid matrix (*rGO/x-CD, x*: *α, β, γ*) by using CV and SWV. The results demonstrated that only *rGO/γ-CD* could trigger an obvious relative potential difference in redox peak. The nanohybrid matrix introduced here is a single material possessing characteristics of both graphene and *CD*, complementing the advantages of one another. The operation principle of such platform can be used as model which can be extended to other chiral analytes.

2. Experimental

2.1. Materials

Graphite powder was obtained from Alfa Aesar. 3,4-dihydroxyphenylalanine enantiomers (*D*- and *L*-DOPA), cyclodextrin derivatives (*α*-, *β*- and *γ*-*CD*) and all other chemicals were purchased from global supplier (Sigma-Aldrich, Germany) and were used without further purification. All aqueous solutions were freshly prepared using Milli-Q ultra-pure water.

2.2. Apparatus

Fourier transformed infrared (FT-IR) spectra were acquired using a Perkin Elmer 100 ATR-FTIR spectrometer between 550 and 4000 cm^{-1}. Raman spectra were recorded between 500 and 3200 cm^{-1} on inVia-Reflex equipped with CCD detector (Renishaw, England). Scanning electron microscopy (SEM) was performed by a ZEISS EVO LS 10 SEM at accelerating voltage of 20 kV and 20.00 kX magnifications. Electrochemical measurements were conducted in a conventional three-electrode cell in A-PBS buffer (50 mM sodium acetate/50 mM phosphate) of pH 7.40 with 100 mM KCl. The bare/modified glassy carbon, platinum and Ag/AgCl/KCl (sat.) electrodes were utilized as working, counter and reference electrode, respectively. The cell was powered by CompactStat potentiostat (Ivium, Netherlands) supported with a C3 electrochemical cell stand (BASi, USA). Super RK 106 (Sonorex, Germany) was used to clean electrode surfaces as ultrasonic bath.

2.3. The synthesis of x-cyclodextrin functionalized reduced graphene oxide (rGO/x-CD)

To prepare graphene based nanosheets combined with *x-CD* derivatives (*x*: *α, β* and *γ*), graphene oxide (*GO*) was freshly synthesized by considering the chemical procedure of a modified Hummers' method [13] with an additional pre-oxidation process as indicated in our previous research [9,14]. Then, *rGO/x-CD* nanohybrids were obtained by the following reported procedure [15]. A 10.0 mL of *GO* solution (0.5 mg/mL) was prepared by sonicating for 60 min to obtain a homogeneous dispersion. Then, 10.0 mL of 40 mg/mL *x-CD* aqueous solution and 150.0 μL of ammonia solution were syringed into the *GO* solution. After addition of 10 μL of hydrazine solution, the mixture was stirred for a few minutes. The resultant mixture was immersed in a water bath (60 °C) for 4 h to obtain a stable black dispersion. The dispersion was filtered using 0.22 μm pore sized membrane filter to obtain *rGO/x-CD* nanohybrids. It should be remarked that, in this design, multiple CDs are anchored onto graphene sheets in a “one pot” reduction process of graphene oxide in the presence of ammonia [16].

2.4. Preparation of modified GCE

In order to prepare the modified glassy carbon electrode (GCE), we polished GCE surfaces by applying the optimized polishing procedure consisting of treatment with alumina slurries of 1.0, 0.3 and 0.05 μm diameter on a wet felt pad, rinsing off twice with ultrapure water between grain sizes. The freshly polished GCE was immersed in water and methanol, respectively, and sonicated in ultrasonic bath for 15 min to remove residual alumina particles. After washing and drying steps, the enantioselective matrix on GCE was prepared by drop-casting of 5.0 μL aqueous solution of *rGO/x-CD* (0.2 mg mL^{-1}). Finally, the modified electrode was dried at room temperature prior to use. The experimental procedure mentioned above was given in Scheme 1.

2.5. Procedure for molecular docking study

AutoDock Vina (ADVina) was utilized to explore the possible binding modes and interaction energies of DOPA enantiomers with *rGO/x-CD* [17]. The crystal structures of *x-CD* (*α*-, *β*- and *γ*-*CD*) were extracted from the protein data bank databases with pdb codes of