Electrochimica Acta 187 (2016) 34–45

Contents lists available at ScienceDirect

Electrochimica Acta

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

An unusual electrochemical oxidation of phenothiazine dye to phenothiazine-bi-1,4-quinone derivative (a donor-acceptor type molecular hybrid) on MWCNT surface and its cysteine electrocatalytic oxidation function

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ARTICLE INFO

Article history:
Received 29 May 2015
Received in revised form 6 November 2015
Accepted 7 November 2015
Available online 10 November 2015

Key words:
Phenothiazine dye
phenothiazine-bi-1,4-quinone
donor-acceptor
multi-walled carbon nanotube
cysteine

ABSTRACT

Phenothiazine (PTZ), a thiazine class heterocyclic compound, is a well-known electron donating system and has been widely used as a starting compound to prepare various phenothiazine dyes and pharmaceutically important compounds. Quinones and its derivatives are constituents of biologically active molecules serve as excellent electron-acceptor systems. Oxidation of PTZ by chemical and electrochemical methods often resulted into monohydroxylation of benzene ring moiety, S-oxidized and polymerized compounds as end products. Electrochemical oxidation of PTZ on a multiwalled carbon nanotube (MWCNT) modified glassy carbon electrode in pH 7 phosphate buffers solution (PBS) has been investigated in this work. A highly redox active surface confined PTZ-bi-1,4-quinone derivative (PTZ-biQ) on MWCNT modified glassy carbon electrode, designated as GCE/MWCNT@PTZ-biQ, as a product was unusually observed. The GCE/MWCNT@PTZ-biQ showed well-defined redox peaks at $E_{1/2} = -0.07$ and +0.29 V vs Ag/AgCl corresponding to surface confined electron-transfer behavior of the bi-quinone (acceptor) and PTZ-cationic radical species (donor) respectively. No such electrochemical characteristics were noticed when unmodified GCE was subjected to the electrochemical oxidation of PTZ. Existence of PTZ-biQ was confirmed by XRD, Raman spectroscopy, FT-IR and GC-MS (methanolic extract of the active layer) analyses. Position of biQ in PTZ-biQ as 1,4-quinone isomer was confirmed by observation of absence of copper-complexation with 1,4-quinone and H_2O_2 electrochemical reduction reactions at −0.1 V vs Ag/AgCl unlike to the specific copper-complexation and H_2O_2 reduction with 1,2-quinone isomer in pH 7. Cysteine (CySH) oxidation was studied as a model system to understand the electron-transfer function of the MWCNT@PTZ-biQ. A highly selective electrocatalytic oxidation and sensing by amperometric i-t and flow injection analysis of CySH at low oxidation potential, 0.3 V vs Ag/AgCl in pH 7 PBS with detection limit values (signal-to-noise ratio = 3) of 11.10 μM and 110 nM respectively, without any interference from other biochemicals like uric acid, dopamine, nitrite, citric acid and H_2O_2, unlike the conventional chemically modified electrodes with serious interference's, have been demonstrated.

1. Introduction

Phenothiazine (PTZ) is a thiazine class heterocyclic compound and has been widely used in the synthesis of various organic dyes such as methylene blue (MB), methylene green, thionine (Th), azure dye (AZ), toludine blue (TB) and certain pharmaceutical drugs like chlorpromazine, prochlorperazine and promethazine [1–3]. It has diverse pharmacology activities which include antituberculosis, antitumor, bactericides etc. It is even helpful in treating Creutzfeldt-Jacob (ncCJD) and HIV diseases [4]. Because of its pharmacological importance, oxidation/reduction mechanisms of PTZ are paramount interest in understanding its pharmacokinetics. It has been reported that PTZ is metabolized by Cytochrome P450 isoforms in human liver and giving rise to ring-hydroxylated, S-oxidized and N-demethylated metabolities [5,6]. Similar kinds of compounds were obtained as reaction products when PTZ was subjected to chemical and electrochemical oxidation in a mixture of aqueous and non-aqueous solvents [7]. However, discreet

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http://dx.doi.org/10.1016/j.electacta.2015.11.032
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electrochemical oxidation of PTZ on conventional electrodes (Pt, glassy carbon electrode (GCE) and Au) either in organic or in aqueous acidic medium or multiwalled carbon nanotube modified electrode in acid medium [8–11] yielded polymeric PTZ as a sole product. For instance, poly-phenothiazine and poly (toluidine blue) were obtained as final products upon the electrochemical oxidation of PTZ and toluidine blue on GCE in DMSO and 0.01 M borate buffer (pH 9.1) + 0.1 M $NaNO_3$ respectively [8,9]. Herein, we report an unusual electrochemical oxidation of PTZ to a highly redox active and surface confined PTZ-bi-1, 4-quinone derivative (PTZ-biQ, biQ=bi-quinone (bi-1,4-quinone)) on a MWCNT modified glassy carbon electrode (GCE/MWCNT@PTZ-biQ) in pH 7 phosphate buffer solution (PBS). To the best of our knowledge, selective electrochemical oxidation of PTZ to PTZ-biquinone like product was never reported in the literature. However, anthraquinone-functionalized PTZ based electron acceptor-donor compounds, prepared by discrete chemical synthetic route, were reported [12].

The combination of donor (D)–acceptor (A) like host–guest pair serves as a good charge-transfer (CT) complexes with fascinating electrochemical and photochemical properties [13]. Quinone acceptor based CT systems are considered to be a best model owing to its mimicking property of the Photosystem I [14]. In past, several fused molecular compounds based on derivatives of Ferrocene (fc) and quinone (Q), as a D–A as self-assembled monolayers (SAM) have been reported and studied as CT [15–17]. Unfortunately, most of the reported D-A systems are redox active either in organic or in acidic medium only. In addition, degradation of the SAM was noticed in the neutral pH solution. The new MWCNT@PTZ-biQ prepared in this work is found to be highly redox active and stable in neutral pH. It is note-worthy that the D-A activity observed with MWCNT@PTZ-biQ is merely due to the PTZ-biQ single molecular unit system, unlike to the previous D–A reports with multi-molecular analogues separated by suitable spacer [15–17]. MWCNT matrix is found to stabilize the D–A single molecular unit unusually in this work.

MWCNT has unique surface feature. The sp^2 carbons of CNT (graphitic carbon) can interact with sp^2 carbons of aromatic organic molecules through pi–pi interaction and make the {CNT-organic compound} hybrid so facile for the low potential electrochemical oxidation to highly redox active compounds [18]. It was found that different isomers of aromatic organic compounds interact differently with CNT's graphitic layer and further to different electro-oxidative products. For example, anthracene and 1,10-phenonthroline get oxidized as anthraquionone and 1,10-phenonthroline-quinone respectively, whereas phenthrene was found to be electro-inactive on MWCNT surface [18,19]. Our interest in this work is to examine the electrochemical behavior of heteroatom substituted anthracene analogue, PTZ on MWCNT surface. As per our previous studies [18,19], it is expected that PTZ will electro-oxidize to PTZ-sulphone, since, the 9,10 positions of the PTZ are occupied by N and S atoms and the S atom is prone to oxidize as sulphone derivative. On the contrary, highly redox active surface confined molecular species (PTZ-biQ) was unusually obtained upon electrochemical oxidation of PTZ on MWCNT in this work. Physicochemical characterizations of GCE/MWCNT@PTZ-biQ by FT-IR, Raman spectroscopy, XRD, GC-MS (methanolic solution) and *in-situ* electrochemical quartz crystal microbalance (EQCM) confirmed the presence of PTZ-biQ in GCE/MWCNT@PTZ-biQ system. Electrochemical oxidation cysteine (CySH) was taken as a model system to study the heterogeneous electro-transfer function of the GCE/MWCNT@PTZ-biQ. This new MWCNT@PTZ-biQ system showed highly efficient electro-catalytic oxidation and electrochemical flow-injection analysis of cysteine (CySH) at low operating potential, 0.3 V vs Ag/AgCl in neutral pH solution.

CySH is an important thiol-containing amino acid that plays crucial role in the metabolism of a number of essential biochemicals mainly biotin, heparin and glutathione etc. [20]. Thus, sensitive and selective determination of cysteine in neutral pH is an important research interest in clinical, pharmaceutical and food chemistry. Due to lack of chromophore, direct detection of CySH by spectroscopic techniques like UV–vis and fluorescence are highly difficult. Alternately, derivatization based analytical methods were often reported for this purpose [21–25]. For instance, phenylisothiocyanate (PTC) [21,22], 9-fluorenylmethoxycarbonyl chloride [23], oxycarbonyl chloride [24], *ortho*-phthaldialdehyde (OPA)/2-mercaptoethanol [26,27] and ninhydrin [28] based UV-Vis, HPLC and fluorescence methods were employed for CySH detection. Although, the above mentioned methods allow to sense cysteine at ∼μM concentration, interference by other organic functional groups such as primary amine and sulfur containing compounds was serious. On the other hand, electrochemical methods offer derivatization-less and selective detection for CySH [29–31]. Nevertheless, problems such as unstable detection current signal and high-over potential are restricting the working electrodes (GCE, Pt, Au, boron doped diamond) for extend to real sample analysis [32–36]. To avoid such problems, specific electrochemical-mediator immobilized chemically modified electrodes were introduced. Following are some of the representative examples for the mediator modified electrodes and its electrochemical-oxidation conditions; prussian blue (PB) [34,35], manganese hexacyanoferrate [36] and copper-cobalt hexacyanoferrate

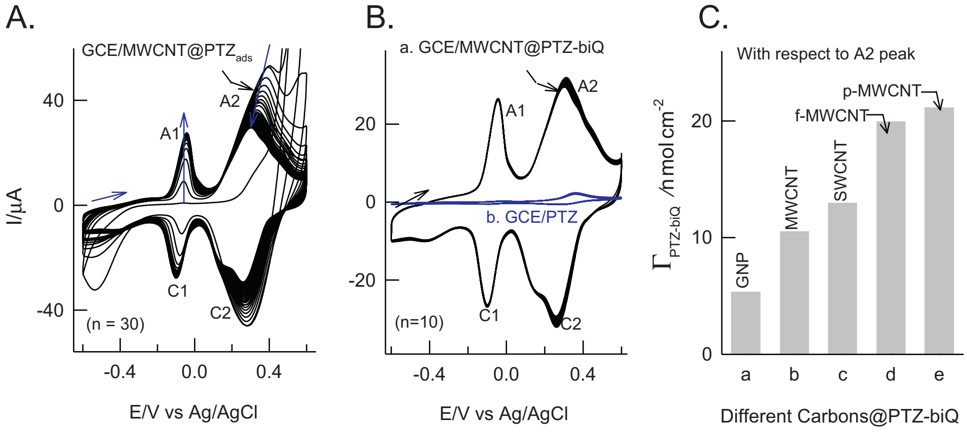

Fig. 1. (A) Thirty continuous CV responses of GCE/MWCNT@PTZ$_{ads}$ in pH 7 PBS at scan rate = 50 mV s^{-1}. (B) Comparative CVs of MWCNT@PTZ-Oxid (a) and bare GCE/PTZ$_{ads}$ (b) in pH 7 PBS. (C) Plot of Γ_{PTZ} versus different carbon materials on the formation of carbons@PTZ-biQ in pH 7 PBS.. Note: PTZ-Oxid = PTZ-biQ, GNP = Graphite nano-powder, f-MWCNT = functionalized-MWCNT and p-MWCNT = purified MWCNT.