



A multidimensional design of charge transfer interfaces via D–A–D linking fashion for electrophysiological sensing of neurotransmitters

He Liu^a, Chaoyi Liu^b, Yue Gu^a, Cong Li^a, Xiaoyi Yan^a, Tingting Zhang^a, Nannan Lu^a, Bo Zheng^a, Yaru Li^a, Zhiquan Zhang^{a,*}, Ming Yang^{c,*}

^a College of Chemistry, Jilin University, Changchun 130012, China

^b State Key Laboratory of Supramolecular Structure and Materials, College of Chemistry, Jilin University, Changchun 130012, China

^c Department of Breast Surgery, First Hospital, Jilin University, Changchun 130012, PR China

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ABSTRACT

Donor–Acceptor (D–A) structure like host–guest pair serves as an organic charge–transfer (C–T) material with pregnant electrochemical and photochemical properties. Phenothiazine, a conjugated nitrogen–sulfur heterocyclic compound with broad pharmaceutical profile, is a strong electron donating system and applied in the synthesis of various classic antipsychotic drugs. In this proposal, a novel D–A molecule, 2,3-bis(4-(10H-phenothiazin-10-yl)phenyl)fumaronitrile (PTBFN), containing a diphenylfumaronitrile as the electrophilic central core and two phenothiazines as the peripheral electron donor functional groups is first designed and synthesized. Subsequently, the C–T layer based on the PTBFN polymer, poly(PTBFN), is obtained via a straightforward electrochemical method and used as an efficient electrocatalyst for dopamine (DA) detection. The logarithm of oxidation peak currents present an outstanding linear response to that of the DA concentration varying from 0.005 to 350 μM with a detection limit down to 0.70 nM, wherein the interferences of uric acid (UA) and ascorbic acid (AA) could be eliminated effectively. Moreover, the biosensor displays decent stability, excellent selectivity for different interfering compounds and applicability in real samples analysis. The favorable sensing performance suggests that the nontrivial D–A architecture is one of the promising bioaffinity catalysts for electrocatalysis and expected to provide wider application potential for biosensing construction and medical diagnostics.

1. Introduction

Dopamine (DA), as a neurotransmitter within the brain, is responsible for the regulation of central nervous, hormonal, cardiovascular as well as renal systems (Heien et al., 2005). Several disorders of the nervous system such as Parkinson's disease (Hirsch et al., 1988), schizophrenia (Grace, 2012) and attention deficit hyperactivity disorder (Wightman et al., 1988) are due to extremely abnormal concentration of DA. Consequently, accurate determination of DA would further a better understanding of these pathophysiological effects and could develop a tool to carry out the output of the treatments. The most elegant techniques for DA determination are high performance liquid chromatography (Park et al., 2013), fluorescence methods (Lu et al., 2011), surface-enhanced Raman scattering (An et al., 2015), colorimetric visualization (Kong et al., 2011). As compared to other analytical methods, electrochemical sensing is an advantageous way for the detection in vivo and in vitro owing to rapid

detection, excellent sensitivity, high selectivity, low cost and ease of operation (Cao et al., 2004; Feng et al., 2017; Guohua et al., 2017; Hu et al., 2017; Hui et al., 2016; Li et al., 2016; Liu et al., 2017; Qin et al., 2016; Zhang et al., 2017, 2016; Zhou et al., 2016; Zou et al., 2017). Nonetheless, considering the low concentration of DA (0.01–1 μM) and the interferences from both electroactive uric acid (UA) and ascorbic acid (AA) in the extracellular fluid, it remains a substantial challenge for quantitative analysis of DA. To surmount these difficulties, various materials have been established such as 2D hexagonal boron nitride (Khan et al., 2016), thiazole-based copolymer (Zhang et al., 2013b) and nanostructured nickel oxide (Roychoudhury et al., 2015) to accurately estimate DA. Progress is being made, the novel material we envisaged is expected to significantly improve sensitivity and selectivity of DA detections.

Conducting polymer film manufactured by electropolymerization of pyrrole, aniline, carbazole, thiophene, and their derivatives, as the flexible electrode materials, have attracted considerable research

* Corresponding authors.

E-mail addresses: zzq@jlu.edu.cn (Z. Zhang), yangming1967@163.com (M. Yang).

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interest in virtue of their natural characteristics (e.g. high electrical conductivity and intriguing redox properties) (Bredas et al., 2002; Chauhan et al., 2017; Cosnier et al., 2003; Mao et al., 2015; Wang et al., 2017). And molecular wire theory is an appealing alternative. Swager et al. demonstrates that the conjugated polymers are interconnecting as a molecular wire and superior over other materials (small molecular-based and inorganic semiconductors) due to their robust conductivity of the backbone in measurable system (Zhang et al., 2013a). Recently, promising emerging materials with donor–acceptor (D–A) architecture have improved the performance of charge–transfer (C–T), conductivity and exciton migration, compared to their parent conjugated polymers (Ullah et al., 2017). In view of these facts, we have reasoned that D–A conjugated polymers can form a new platform for the signal-enhancing by mediating a fast electron transfer between the analyte and an electrode system. D–A structure capable of ambipolar charge (electron and hole) has been explored as C–T materials in organic light-emitting diode (Kraft et al., 1998), electrochromism (Lv et al., 2017), photovoltaic cells (Sonmez et al., 2005) and organic thin film transistors (Champion et al., 2010). However, its applications in electrochemical sensors are less reported (Kumar et al., 2014).

Inspired by the success in constructing appropriate D and A building blocks, phenothiazine unit has drawn our attention, owing to it possesses the π -delocalization in the central ring cation radical. Some studies have reported that phenothiazine had a fused tricyclic structure similar to that of carbazole, was a stronger and potentially better electron donor than the carbazole unit due to its 0.7 eV lower ionization potential (Kulkarni et al., 2010, 2005; Yao et al., 2014). In addition, a three-carbon chain among the nitrogen atom of the phenothiazine core and the terminal nitrogen of the side chain is the pivotal feature in relation to psychotropic activity (Sudeshna and Parimal, 2010). The phenothiazine group of drugs are used for clinical treatment of psychosis for more than sixty years and primarily to regulate the dynamics of fluctuating DA concentrations (Ohlow and Moosmann, 2011). Because of these characteristics, the functionalized phenothiazine-based molecules, which have been employed as potent pharmacophoric section in pharmacology and biomedicine (Pluta et al., 2011a), may be served as novel electrocatalysts for electrochemical detection of DA. Firstly, the non-planar phenothiazine ring conformation hinders π -stacking aggregation in the polymer main-chains or interaction among analytes, creating a biomimetic microenvironment for the electrochemical recognition process (XX et al., 2003). Secondly, the strong electron-donating property of phenothiazine gives the polymer a low oxidation potential and an enhanced electrocatalytic activity (Jo et al., 2014). Thirdly, the unique biological activities of phenothiazines on biological systems may be able to exhibit high affinity molecular recognition for DA (Mocko et al., 2010; Pluta et al., 2011b). Diphenylfumarionitrile unit displays distinct advantages as acceptor building block for constructing C–T materials with its two cyano functionalities (Shen et al., 2013). It can provide an extended π -conjugated system and effectively reduce the bandgap. Katz and co-workers also used diphenylfumarionitrile building block to achieve an electron mobility of $0.027 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ for vacuum deposited thin film (Lee et al., 2009).

As a proof of concept, 2,3-bis(4-(10H-phenothiazin-10-yl)phenyl)fumarionitrile (PTBFN), a novel π -conjugated D–A compound bestows PTBFN with enhanced intramolecular C–T property, has been first designed to provide great electron delocalization all over the conjugated branches through the whole molecule. And then its conjugated oligomer is gained after a facile electrochemical method. When the electronic and biocompatible properties investigated by our previous studies for selective donor and acceptor units extrapolate to conjugated oligomers with D–A–D linking fashion, two main functions exquisitely influence the analytical performance for DA, namely: (1) The introduced D–A based biosensor is a signal-enhancing system, which relies on amplification by the collective minor current change and accelera-

tion by energy transfer between the DA and electrode surface. (2) An ingenious design of phenothiazine donor, which has maintained non-planar phenothiazine ring, can be as a biorecognition element for specific detection of DA against AA, UA and other analogous endogenous compounds. All above factors endow the biosensor with completely new performance and characteristics.

2. Experimental

2.1. Reagents and apparatus

This section can be found in the [Supplementary material](#).

2.2. Synthesis of the PTBFN monomer

The prepared route of PTBFN was elucidated by [Scheme S1 \(Supporting Information\)](#). PTBFN was synthesized according to a Suzuki coupling reaction between corresponding phenothiazine and 2,3-bis(4-bromophenyl)fumarionitrile. The starting compound 2,3-bis(4-bromophenyl)fumarionitrile (A) was prepared by reacting 4-bromophenylacetonitrile according to the previous reports (Yeh et al., 2003). The mixture of A (3.0 mmol), phenothiazine (6.6 mmol), sodium tert-butoxide (3.6 mmol), toluene (40 mL), tri-*tert*-butylphosphine tetrafluoroborate (0.142 g) were dissolved and degassed before $\text{Pd}_2(\text{dba})_3$ (0.0474 g) was added under nitrogen. The resulting solution was stirred for 48 h at 110 °C and cooled to room temperature. It was then poured into 50 mL water to the reaction mixture and the product was extracted with CH_2Cl_2 for three times. Removal of the solvent afforded the crude product, which was further purified using column chromatography on silica gel (a mixture of petroleum ether/ CH_2Cl_2 = 3:1 as eluent) to give the product as a bright red solid (yield 20%).

2.3. Sensor fabrication

Prior to modification, the bare GCE was polished successively in 1.0, 0.3 and 0.05 μm alumina slurries on microcloth pads. Then, it was sonicated successively in 1:1 nitric acid, ethanol and water, each for 1 min, and dried under a stream of nitrogen. The electrode surface derivatization was carried out in *N,N*-dimethylformamide/acetonitrile = 3:2 (v/v) solution containing 1.000 mg mL^{-1} PTBFN and 100.0 mM lithium perchlorate as a supporting electrolyte through consecutive cyclic voltammetry by scanning the potential from -1.2 – 2.0 V (versus Ag wire) at 0.1 V s^{-1} for 15 cycles. The electrode was then removed and washed with large volumes of acetonitrile.

3. Results and discussions

3.1. Electropolymerization of PTBFN

The mechanism for the electropolymerization of PTBFN and corresponding control experiments are described in the [Supplementary material](#).

3.2. Characterizations of PTBFN monomer and poly(PTBFN) film

[Fig. S5](#) offers ^1H NMR spectrum of PTBFN. ^1H NMR (500 MHz, DMSO): δ = 7.90 (d, J = 8.6 Hz, 4H), 7.42 (d, J = 7.7 Hz, 4H), 7.35 (d, J = 8.7 Hz, 4H), 7.31–7.25 (m, J = 7.7 Hz, 4H), 7.20–7.14 (m, J = 7.5 Hz, 4H), 7.04 (d, J = 8.0 Hz, 4H).

As observed in [Fig. 1a](#), most of the IR frequencies in the spectra of polymer are close to those of its parent monomer with only a little indication of changing of aromatic ring substituents in the range of 900 – 700 cm^{-1} (Schlereth and Karyakin, 1995). The absorption band for the monomer at 1611 cm^{-1} attributed to the C=C stretching vibration of aromatic ring and that at 1382 cm^{-1} corresponding to the tertiary amino group stretching vibration shift to 1621 cm^{-1} and

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