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Electrochemical sensing of heavy metal ions with inorganic, organic and bio-materials

Lin Cui, Jie Wu, Huangxian Ju*

State Key Laboratory of Analytical Chemistry for Life Science, Department of Chemistry, Nanjing University, Nanjing 210093, PR China

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ABSTRACT

As heavy metal ions severely harm human health, it is important to develop simple, sensitive and accurate methods for their detection in environment and food. Electrochemical detection featured with short analytical time, low power cost, high sensitivity and easy adaptability for in-situ measurement is one of the most developed methods. This review introduces briefly the recent achievements in electrochemical sensing of heavy metal ions with inorganic, organic and bio-materials modified electrodes. In particular, the unique properties of inorganic nanomaterials, organic small molecules or their polymers, enzymes and nucleic acids for detection of heavy metal ions are highlighted. By employing some representative examples, the design and sensing mechanisms of these electrodes are discussed.

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* Corresponding author. Tel./fax: +86 25 83593593.
E-mail address: hxju@nju.edu.cn (H. Ju).

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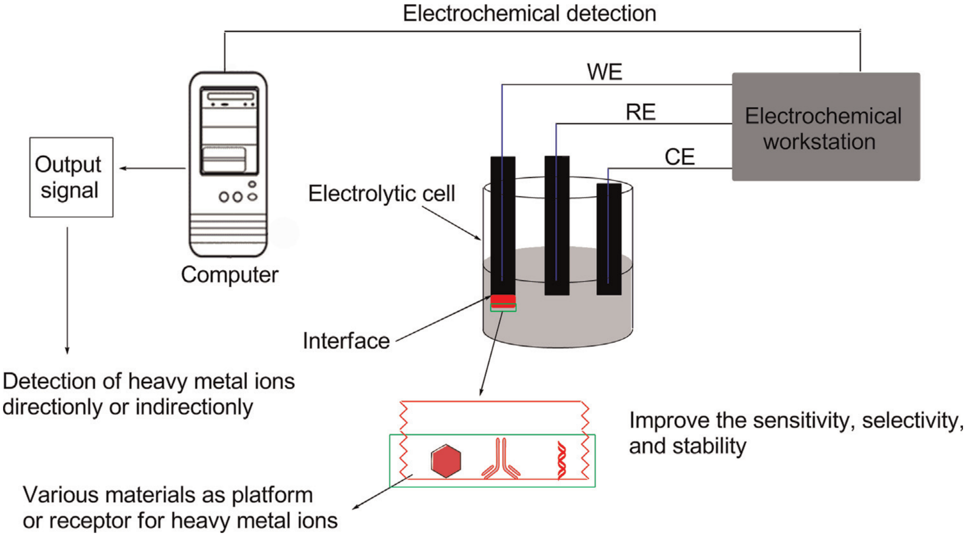

Fig. 1. Schematic illustration of general principle of electrochemical sensing of heavy metal ions.

1. Introduction

Since heavy metal ions are non-biodegradable and can be accumulated in soft tissues, they are considered as the serious source to pollute the biosphere throughout the world and cause many healthy and physiological diseases (Kemper and Sommer, 2002; Tu et al., 2004; Tuzen et al., 2006). Therefore, sensitive and selective determination of toxic heavy metals with a cost-effective and convenient procedure is paramount important. Various techniques have been developed for the detection of heavy metal ions, including electrochemical (Aragay and Merkoçi, 2012), mass spectrometric (Ugo et al., 2001) and optical methods (Kim et al., 2012). For example, atomic absorption spectrophotometry (AAS) has been widely used for the detection of metal ions in industry. This technique can simultaneously detect different ions with high sensitivity, selectivity and accuracy. However, it requires relatively expensive instrument and specialized personnel to carry out the operational procedures. Due to the capability of short analytical time, low power cost, high sensitivity and easy adaptability for in-situ measurement (Wong et al., 2007), electrochemical detection methods have attracted great interest in the detection of heavy metal ions.

The electrochemical detection is normally performed with a three-electrode system containing a working electrode (WE), a reference electrode (RE) and a count electrode (CE) (Fig.1). The WE can be modified with different materials for specific recognition or/and concentration of metal ions (Bontidean et al., 1998; Pan et al., 2009). The presence of heavy metal ions causes the change of current, potential, electrochemical impedance, capacitance or electrochemiluminescence, which can then be used for their detection (Combellas et al., 2008; Fan et al., 2009). Based on these detection signals, the electrochemical sensings can be classified to amperometric, potentiometry, electrochemical impedance, capacitance and electrochemiluminescent methods.

Recent advances in new materials, especially the development of nano- and bio-materials, have opened a new era of analytical techniques. In particular, due to their unique electronic, physical, chemical and mechanical properties, nano- and bio-materials have been explored their extensive applications in electrochemistry (Zhang and Fang, 2010). By tailored functionalization and assembly, these materials can be easily assembled on electrode surface for the fabrication of sensing electrodes and the sensitive and selective detection of heavy metal ions. The assembly of different materials can further improve the electrochemical performance. For example, polymers or biomaterials are frequently assembled on inorganic nanomaterials to construct the highly sensitive electrochemical sensors for heavy metal ions (Chey et al., 2012; Gong et al., 2010; He et al. 2011; Kong et al., 2009; Liu et al., 2010; Pan et al., 2009; Sánchez et al., 2010; Shao et al., 2012; Sudibya et al., 2011; Tang et al., 2013; Wang et al., 2012). This review discusses the design and sensing mechanisms of these electrochemical sensors and introduces the recent advances in electrochemical sensing of heavy metal ions. For clear illustration, the sensing strategies are classified into inorganic, organic and biomaterials modified electrodes, in which the hybrid materials are introduced respectively.

2. Inorganic nanomaterials for electrochemical sensing of heavy metal ions

Benefiting from the intrinsic advantages of regular structure, chemical and thermal stability, high surface reaction activity and catalytic efficiency, large surface-to-volume ratio and strong adsorption ability (Kaushik et al., 2008), inorganic nanomaterials are often used for electrode modification. In particular, metal, metal oxide, carbon and silica based nanomaterials are the most commonly used inorganic nanomaterials in electrochemical detection of heavy metal ions.

2.1. Metal nanoparticles

Metallic nanostructured materials exhibit unique electrical, optical and catalytic properties. Meanwhile, by functionalizing metallic nanoparticles with small chemical and bio-molecules, various detection methods with high specificity have been designed for heavy metal sensing.

Early electroanalytical methods frequently employed the hanging mercury drop and mercury-film based electrodes to detect the heavy metals, because of their wide cathodic potential range, high sensitivity and repeatability (Ensafi et al., 2004; Shams et al., 2004). With the increasing concern about the toxicity of mercury to the environment and the difficulty in handling, storage, and disposal, the use of mercury as an electrode material was banned, and mercury-free solid-state electrodes, such as bismuth and stannum based electrodes, emerged for heavy metals detection. By co-deposition of bismuth and target metals on the glassy carbon or carbon-fiber substrate, bismuth-film electrodes could be obtained for stripping voltammetric measurements of Cd^{2+}, Pb^{2+}, Tl^{3+}, and Zn^{2+} at mg L^{-1} level (Wang et al., 2000). Recently, a nanocomposite of reduced graphene oxide–bismuth nanoparticles (RGO/Bi) has been synthesized for sensitive detection of multiple heavy metals, in which the detection limits of 2.8, 0.55, 17 and 26 μg L^{-1} are obtained for Cd^{2+}, Pb^{2+}, Zn^{2+} and Cu^{2+}, respectively (Sahoo et al., 2013). Similar to bismuth, antimony nanoparticles have also been proven to be highly sensitive and reliable for tracing analysis of heavy metals in conjunction with anodic stripping voltammetry (ASV). For example, Toghill et al. (2009) prepared an antimony nanoparticles modified boron doped diamond electrode for simultaneous electrochemical determination of Pb^{2+} and Cd^{2+} over the range of 50–500 mg L^{-1}.

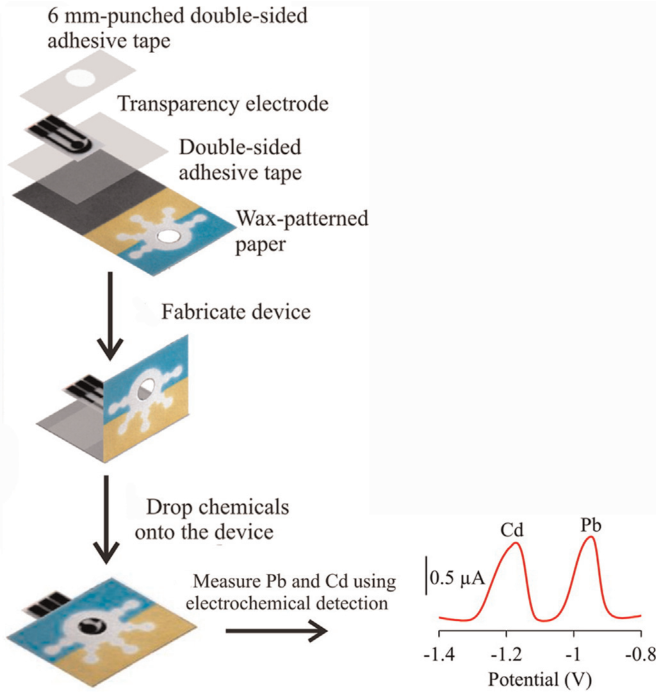

Fig. 2. Schematic drawing of the fabrication procedure for paper-based analytical devices and ASV detection of Pb^{2+} and Cd^{2+} (reproduced from Rattanarat et al. (2014) by permission of the American Chemical Society).

In addition, nanosized noble, bimetallic and transition metal particles modified electrodes have emerged for electrochemical analysis of heavy metals (Berchmans et al., 2008; Dai et al., 2004; Dai and Compton, 2006; Ouyang et al., 2012). By layer-by-layer assembly, multi-layer of Au nanoparticles (AuNPs) can be immobilized on the surface of gold electrode to construct sensitive sensor for As^{3+} detection (Ottakam Thotiyl et al., 2012). Combining with ASV detection, this sensor can detect 4.36 μg L^{-1} level of As^{3+}, which is lower than the World Health Organization (WHO) guideline of 10 μg L^{-1}. Based on the facile wet-chemical process, a composite of bimetallic Au–Pt nanoparticles/organic nanofibers with uniform three-dimensional porous nanostructure has been prepared (Gong et al., 2010). Benefiting from the large effective surface area and good conducting property of the nanocomposite, this sensor shows a low detection limit of 0.008 μg L^{-1} for Hg^{2+}. In addition, these metal particles have also been utilized for microarray fabrication. For example, the AuNPs-based microelectrode ensembles have been proven to be promising in the detection of heavy metals (Abollino et al., 2008; Chemnasiry and Hernandez, 2012; Kumar Jena and Retna Raj, 2008; Orozco et al., 2008).

For real application, more and more heavy metal electrochemical sensors have been fabricated on screen-printed carbon electrode (SPCE) due to its nature of inexpensiveness, portability and easy to mass production (Niu et al., 2013; Song et al., 2010). For example, by electrodepositing AuNPs on SPCE, Liu et al. (2007) fabricated a disposable sensor for the detection of Cr^{6+} in river water. Currently, based on screen-printed technology, easy made devices, such as paper-based analytical device, have been developed for heavy metal detection (Rattanarat et al., 2014; Zhang et al., 2013). For example, the device fabricated by screen-printing multi-walled carbon nanotubes (MWCNT) mixed carbon inks on polyester and then modified with Bi nanoparticales and ferricyanide has been proposed to enhance stripping signals and reduce Cu^{2+} interference (Rattanarat et al., 2014) (Fig. 2). The top layer of the device contains five wax-defined channels extending outward from an open sample reservoir. In order to obtain high selectivity and sensitivity, each channel contains individual sample pretreatment and detection zones. Under the optimized conditions, such

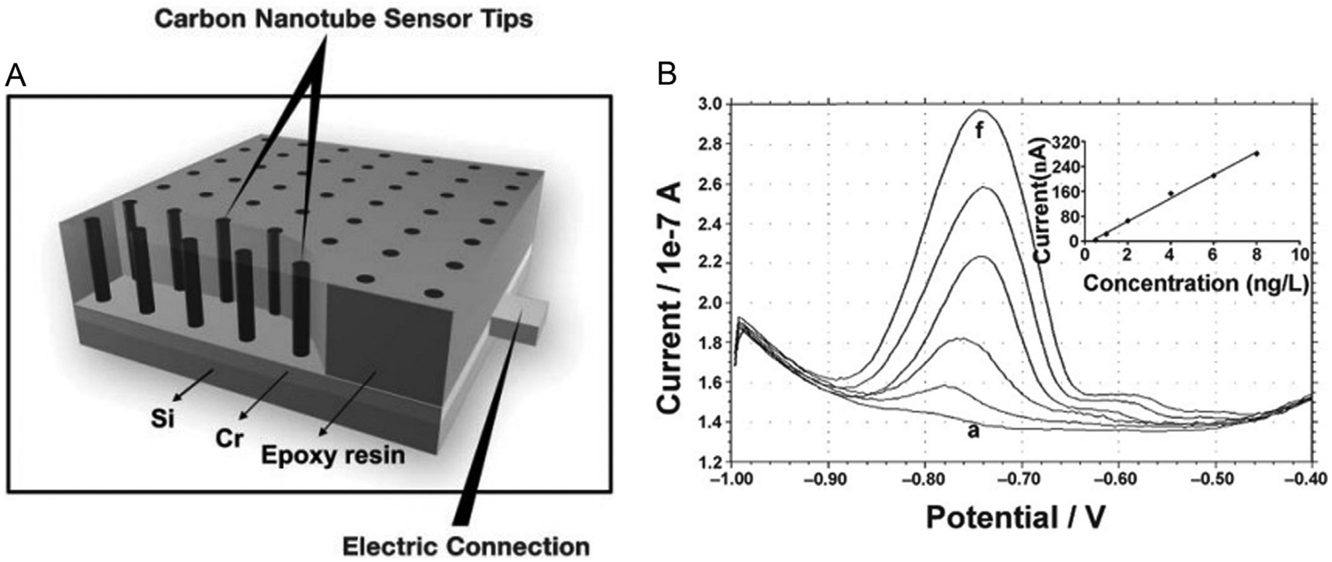

Fig. 3. (A) Structure and (B) SWV response of CNT-NEA to Cd^{2+} (0.5, 1, 2, 4, 6, 8 mg L^{-1}). Inset: calibration plot. The bismuth-coated CNT-NEA is in situ prepared with 1-min pretreatment at 0.3 V, 2-min accumulation at 21.2 V, 10-s rest period (without stirring). SWV scan: step potential, 5 mV; amplitude, 20 mV; frequency, 25 Hz (reproduced from Liu et al. (2005) by permission of the Royal Society of Chemistry).

paper-based device can simultaneously detect Cd^{2+} and Pb^{2+} in the range of 5–150 μg L^{-1}.

Besides the ASV-based detections, recently, Cho et al. (2012) designed a class of solid-state sensors for the detection of CH_3HgC by measuring the tunneling current of nanoparticles. These sensors were fabricated with films of nanoparticles which were protected with striped monolayers of organic ligands. This method could detect CH_3HgC in both standardized solutions and environmental samples with simple operation, high sensitivity and short assay time.

2.2. *Metal oxides*

Nanostructured metal oxides such as ZnO, Fe_3O_4, NiO, SnO_2, ZrO_4, TiO_2, MgO and MnO_2 have also been widely used in the detection of heavy metals due to their interesting nano-morphological, functional biocompatible, non-toxic and catalytic properties. These materials exhibit enhanced electron-transfer kinetics and strong adsorption capability. For example, porous MgO nanoflowers have been synthesized to fabricate heavy metal sensitive electrode (Wei et al., 2012). By combining with square wave anodic stripping voltammetry (SWASV), the modified electrode exhibits excellent sensing performance for Pb^{2+} and Cd^{2+} with detection limits of 2.1 pM and 81 pM, respectively. Yantasee et al. (2008) synthesized dimercaptosuccinic acid-functionalized Fe_3O_4 nanoparticles to modify carbon electrodes for detection of Pb^{2+} in urine and simultaneous detection of Cu^{2+}, Pb^{2+}, Cd^{2+} and Ag^{+} in natural water. By combining the high absorptivity of Fe_3O_4 microspheres toward As^{3+} and the advantages of ionic liquid, Gao et al. (2013b) reported a disposable platform for electrochemical detection of As^{3+} at 8×10^{-4} μg L^{-1} level in drinking water under nearly neutral condition. Wu et al. (2012) synthesized NiO nanosheets with uniformly distributed mesoporosity by calcination of β-$Ni(OH)_2$ nanosheet precursor for selective electrochemical detection of Hg^{2+}. Liu et al. (2010) fabricated an electrochemical sensor for lead ion with DNA-based vertically aligned conductive carbon hybridized TiO_2 nanotube arrays (DNA/C-TiO_2 NTs). This sensor possessed a wide linear calibration ranging from 0.01 to 160 nM with the detection limitation at picomole level (3.3 pM).

2.3. *Quantum dots (QDs)*

QDs are bright and photostable materials with broad excitation spectra but narrow Gaussian emission superior to conventional organic fluorescence dyes, and can be tunable in a wide emission range from UV to NIR due to the quantum size effect (Gill et al., 2008). Their application in electrochemiluminescent (ECL) sensing is of considerable interest since the first ECL sensor based on CdSe QDs was reported in 2004 (Zou and Ju, 2004). Recently, Cheng et al. (2010) observed the presence of Cu^{2+} could quench the ECL emission of CdTe QDs, hence, designed a low-potential ECL method for detection of Cu^{2+}. However, due to the toxicity of QDs, QDs are rarely used to detect heavy metals.

2.4. *Carbon nanotubes*

Nanoscale carbon-based materials such as carbon nanoparticles, CNTs, fullerenes and graphene (GR) exhibit many excellent electric properties, which make them ideal candidates as electrode materials in heavy metal detection. Normally, they act as adsorbent/preconcentrator agent and transducer platform. CNTs have become one of the most interesting materials since they were invented in 1991. Numerous investigations have been carried out to explore the potential applications of CNTs, due to their advantages such as large effective detection surface, high electron transfer rate, high electrocatalytic activity and low electrode fouling. They can response to both organic and inorganic analytes (metal cations) (Guo et al., 2011; Oztekin et al., 2011; Tarley et al., 2009). Bui et al. (2012) used gold nanoparticles deposited carbon nanotube film to perform electrochemical detection of Pb^{2+} and Cu^{2+}. By SWASV measurements, this method could simultaneously detect Pb^{2+} and Cu^{2+} with the detection limits of 0.546 and 0.613 μg L^{-1}, respectively. The selectivity and sensitivity of heavy metal detection could be enhanced by functionalization of CNTs (Mohadesi et al., 2010).

CNTs have also been employed to prepare nanoelectrode arrays (NEAs) (Fig. 3A) by using plasma-enhanced chemical vapor deposition (Liu et al., 2005). CNTs-NEAs have the properties of low background current and a high signal-to-noise ratio, and can be used for ultrasensitive voltammetric detection of trace Cd^{2+} and Pd^{2+}. Fig. 3B displays the SWASV response of aligned nanotube NEA for increasing Cd^{2+} concentrations in the range from 0.5 to 8 mg L^{-1} with the detection limit of 0.04 mg L^{-1}.

2.5. *Graphene*

GR is a two-dimensional and single-atom-thick carbon material. With the unique morphology and properties, such as high thermal conductivity, strong mechanical strength, excellent electronic transport properties, and high surface area, GR has been widely used in biological and chemical sensing (Novoselov et al., 2005). Graphene-based sensors have been widely used for detection of heavy metals (Chang et al., 2014). A SnO_2/RGO nanocomposite with highly uniform size (Fig. 4A) has been used to modify electrode and fabricate sensor for heavy metal detection (Wei et al., 2011). As the SnO_2/RGO nanocomposite can act as electrochemical catalyst in detecting heavy metal ions with SWASVs, the sensor can simultaneously detect Cd^{2+}, Pb^{2+}, Cu^{2+}, and Hg^{2+} with the limits of detection of 0.1, 0.18, 0.23, and 0.28 nM, respectively (Fig. 4B), which are much lower than the guideline value given by WHO.

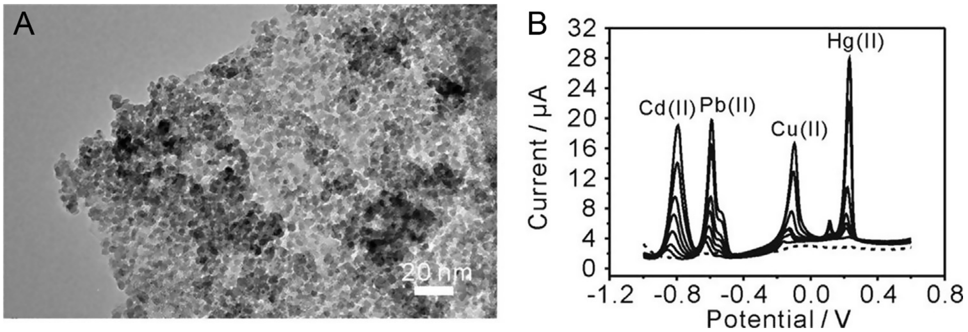

Fig. 4. (A) TEM image of SnO_2/reduced graphene oxide nanocomposite and (B) its SWASV response on GCE for simultaneous analysis of Cd(II), Pb(II), Cu(II), and Hg(II) at 0, 0.3, 0.4, 0.5, 0.6, 0.7, 0.9, and 1.2 μM (from bottom to top) (reproduced from Wei et al. (2011) by permission of the American Chemical Society).

As the cousin of carbon nanotubes, various strategies devised to functionalize CNTs can be adopted straightforwardly for GR. The surface of GR can be covalently created with chemical moieties, commonly, carboxylic (–COOH) and hydroxyl (–OH) groups with strong acids and/or oxidants. Then, the functional molecules with recognition elements to heavy metal ions can be immobilized onto graphene through their reaction with –COOH or –OH (Li et al., 2009). For example, Sudibya et al. (2011) have combined reduced graphene oxide-field effect transistor (RGO-FET) sensor with different probes of metallothione in type II proteins as the conducting and sensing channel for sensitive detection of Hg^{2+} and Cd^{2+}.

2.6. *Mesoporous silica*

Hybrid mesoporous silica nanoparticles (MSNs) are known as their controllable morphologies, porosities, biocompatibility, biodegradability, and ease of functionalization (Sierra and Pérez-Quintanilla, 2013). MSNs are a particular group for electroanalysis of heavy metal. As non-conductors, MSNs do not contribute to the charging current when they are used as an electrode modifier, thus leading to low background. In addition, MSNs cannot be reductively accumulated even at large negative reduction potentials (Zhang et al., 2012). By coating 5-mercapto-1-methyltetrazole derivative functionalized MSNs on SPCE, Sánchez et al. (2010) developed a disposable Pb^{2+} sensor which could quantify Pb^{2+} in the range of 1–30 μg L^{-1} with a limit of detection of 0.1 μg L^{-1}. In addition, N,N'-bis(3-(2-thenylidenimino)propyl)piperazine coated MSNs have been used to modify carbon paste electrode (CPE) and prepare a sensor for detection of multiple ions, such as Cd^{2+}, Cu^{2+} and Hg^{2+} (Afkhami et al., 2013). Although the CPE-based ion sensors are cheap and easy to operation and regeneration, they suffer from the poor inter-batch repeatability. A graphite–polyurethane composite electrode along with the modifier of MSNs organofunctionalized with 2-benzothiazolethiol has been reported to have good repeatability and long-term stability (Cesarino et al., 2010). Under optimal conditions, this modified electrode can detect Cd^{2+}, Pb^{2+}, Cu^{2+} and Hg^{2+} simultaneously in natural water, and exhibits the detection limits down to nanomolar level.

Except for the inorganic nanomaterials aforementioned, many other materials have also attracted attention in the analysis of metal ions. For instance, graphitic-carbon nitride (C_3N_4) has been reported to have more active reaction sites than other N-doped carbon materials and can be used as a good substrate for the fabrication of Pb^{2+} sensors (Wang et al., 2013). In addition, Sadhukhan and Barman (2013) synthesized two-dimensional C_3N_4 under microwave irradiation to modify glassy carbon electrode (GCE) for the detection of Hg^{2+}. Due to its graphene-like structure, this sensor could detect Hg^{2+} down to 0.09 nM.

3. Organic materials for electrochemical detection of heavy metal ions

3.1. *Organic small molecules*

Organic molecular ligands are widely used in the preparation of ion sensors due to their specific recognition of metal ions (Chen et al., 2011; Oztekin et al., 2011). The interaction between heavy metals and organic ligands follow the Pearson hard–soft, acid–base (HSAB) theory, in which the soft acids react faster, and form stronger bonds and more stable complexes, with soft bases and vice versa (Parr and Pearson, 1983; Pearson, 2005). Thus, the metal ions such as Hg^{2+}, Cd^{2+}, Ag^{+}, etc., which are classified as soft acids, tend to bind preferentially with ligands containing S (e.g. thiol groups), whereas Cr^{3+} and Al^{3+}, classified as hard acids, prefer the coordination with ligands containing oxygen. The borderline acids (Pb^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+}, etc.) prefer to bind to ligands containing N donor atoms. Based on this theory, L-cysteine self-assembled monolayer modified gold electrodes have been fabricated to detect of Cu^{2+} with stripping analysis (Yang et al., 2001). This method can detect Cu^{2+} with a detection limit of below 5 μg L^{-1}. Another example is the interaction of Cd^{2+} with glutathione, which has been used for Cd^{2+} detection (Chow et al.,

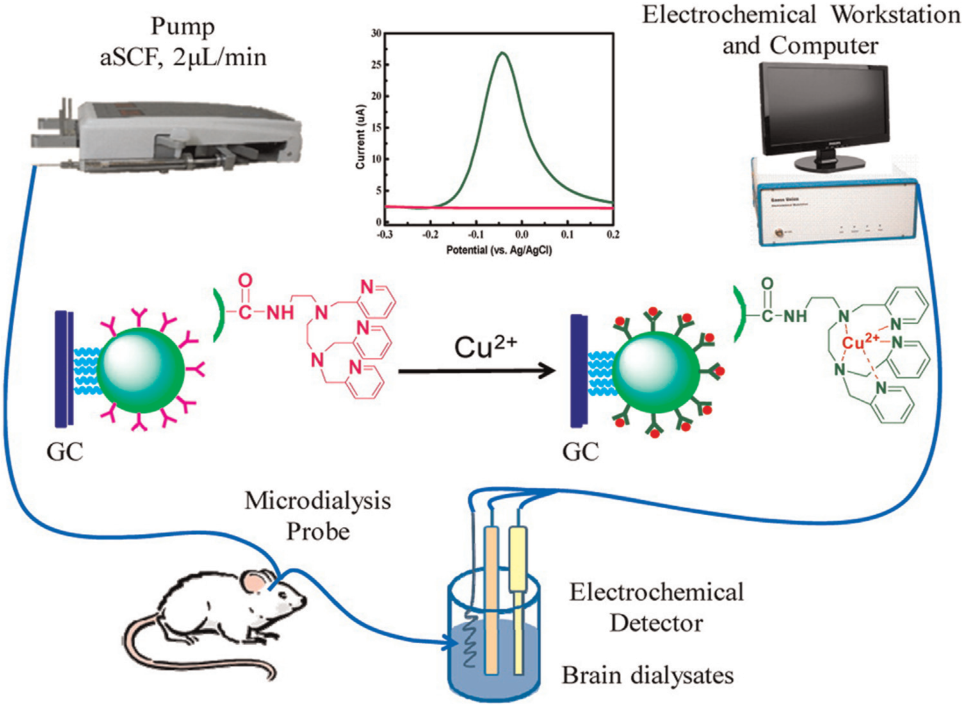

Fig. 5. Schematic illustration of electrochemical method for monitoring cerebral Cu^{2+} in rat brain microdialysates (reproduced from Shao et al. (2012) by permission of the American Chemical Society).

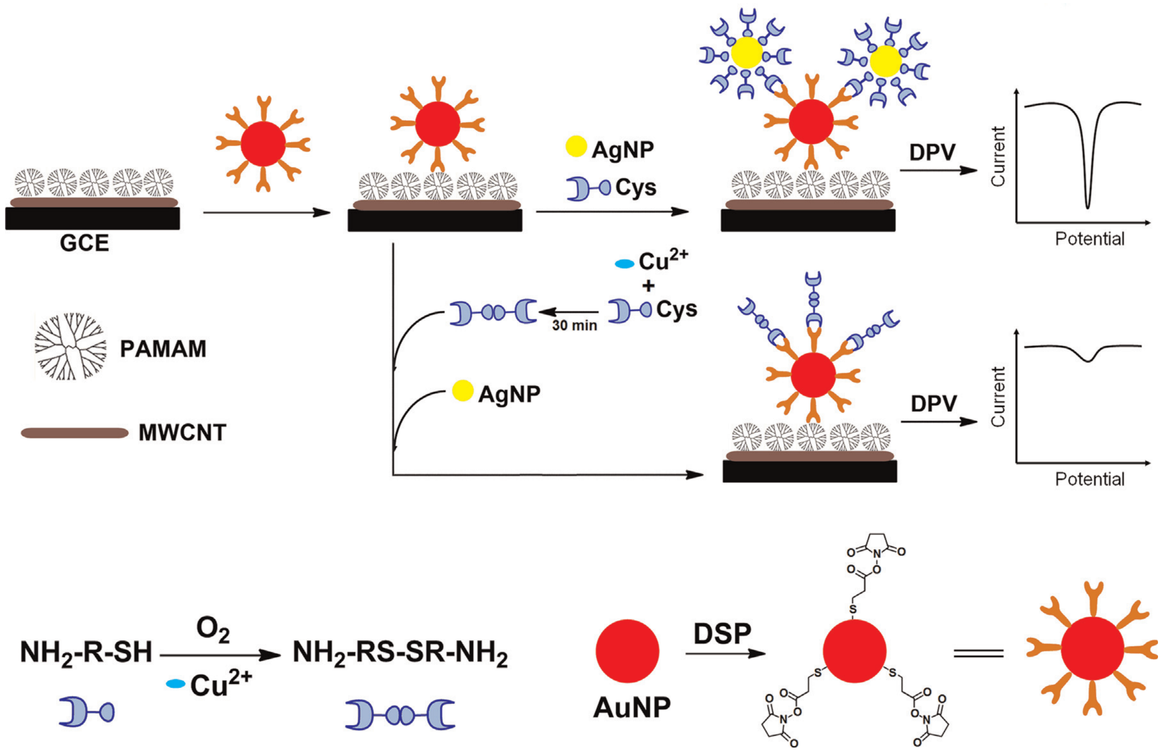

Fig. 6. Schematic diagram of electrochemical detection of Cu^{2+} based on Cu^{2+}-catalyzed oxidation of Cys to disulfide cystamine by O_2 (reproduced from Cui et al. (2014) by permission from Elsevier Science Ltd. UK).

2005). The modified electrode can be regenerated with a detection limit of 5 nM for Cd^{2+}.

Generally, organic molecular ligand modified inorganic nanomaterials can be used to fabricate electrochemical ion sensors. For example, based on the high affinity between N-(2-aminoethyl)-N,N′,N′-Tris(pyridine-2-yl-methyl)ethane-1,2-diamine (TPEA) and Cu^{2+}, Shao et al. (2012) used TPEA functionalized carbon dots (C-Dot-TPEA) nanocomposites to prepare a sensitive Cu^{2+} sensor (Fig. 5). With the amplified property of C-Dots, the sensitivity of this sensor was increased. The developed method made its use in the determination of Cu^{2+} in the complex brain system with electrochemical strategy.

Besides the HSAB-based coordination, some electrochemical ion sensors are also prepared based on the catalytic ability of heavy metal to organic reaction. The most remarkable reaction is the click reaction catalyzed with copper(I), referring as azide–alkyne cycloaddition reaction (CuAAC). CuAAC owns several significant advantages, such as fast and facile reaction, mild reaction conditions (such as aqueous solvent), water and air insensitivity, high quantitative and purity yields, and has been used to construct high efficient ECL (Qiu et al., 2011a) and amperometric (Qiu et al., 2011b) methods for Cu^{2+} detection. These methods exhibit very low detection limits down to fM level, however, the pair of alkyne and azide groups as well as a reduction process of Cu^{2+} to Cu^{+} are required, which limits their practical application. Based on the copper-catalyzed oxidation of thiol compounds (R–SH) to disulfide compounds (R–S–S–R), our group recently developed a convenient and highly sensitive electrochemical method for the copper detection (Cui et al., 2014). In the assay, the sensor was prepared on a GCE by layer-by-layer modification with MWCNTs, poly (amidoamine) dendrimers and dithiobis[succinimidyl-propionate] encapsulated AuNPs (DSP-AuNPs) (Fig. 6). The DSP-terminated sensor could capture cysteamine (Cys) functionlized AgNPs through the reaction between DSP and Cys. The presence of Cu^{2+} catalyzed Cys to cystamine, and hence, regulated the assembly of AgNPs on the surface of sensor, resulting in the decrease of electrochemical stripping signal of AgNPs. With this strategy, the method could detect Cu^{2+} in the range of 1.0–1000 nM with a detection limit of 0.48 nM.

3.2. *Organic polymers*

By copolymerization of monomers and post-modification of polymerized products on electrodes, a large number of organic polymers, particularly conducting and chelating polymers, have been used to construct ion sensors. The most commonly used conducting polymer includes polyacetylene (PAc), polyaniline (PANI), polypyrrole (PPy), poly(p-phenylene) (PPP), polythiophene (PTh), and poly(3,4-ethylenedioxythiophene) (PEDOT) (Kumar et al., 2012; Manisankar et al., 2008; Yasri et al., 2011). Commonly they are combined with inorganic nanomaterials to fabricate sensitive sensors for heavy metals. For example, with thiol groups of poly(2,5-dimercapto-1,3,4-thiadiazole) (PDMcT) to bind Cd^{2+} and Pb^{2+}, He et al. (2011) combined PDMcT with MWCNTs to modify GCE for analysis of Cd^{2+} and Pb^{2+}. Due to the improved binding ability of PDMcT and the function of MWCNTs, the limits of detection ($S/N=3$) for Cd^{2+} and Pb^{2+} were 0.03 and 0.05 $\mu g\ L^{-1}$, respectively.

The selective polymeric membranes, which minimize matrix interferences, are also used in the potentiometric sensors for heavy metal detection. They are the main part of the well-known ion-selective electrodes (ISEs) (Gupta et al., 2011a; Zuliani and Diamond, 2012). Gupta et al. (2011b) reported a coated-wire ISE based on iron-cyclam complex for the determination of Fe^{3+} by ion-selective potentiometry. The wide range was found to be 10 mM to 1.0 μM. Another Cu^{2+} solid-contact ISE was developed using 1,2-di-(o-salicylaldiminophe-nylthio) ethane as a neutral carrier to mix with carbon ink (Brinić et al., 2012). The electrode was suitable for determination of Cu^{2+} with a wide linear range. The introduction of nanostructured material as transducer in ISEs led to new types of potentiometric sensors. For example, Pan et al. (2009) developed a Pb^{2+} ISE using 4-tert-butylcalix[4]arene-tetrakis(N,N-dimethylthioacetamide) coupled with nanosized hydroxyapatite (NHAP). The sensitivity and detection limit of the proposed sensor were 13 μA μM^{-1} and 1.0 nM, respectively.

In addition, ion-imprinting polymers (IIP), which possess specific recognition sites and high affinity, are also used for heavy metal sensing (Rao et al., 2006). Alizadeh and Amjadi (2011) prepared a CPE modified with nano-sized Pb^{2+} imprinted polymer by copolymerization of methacrylic acid–Pb^{2+} complex and ethylene glycol dimethacrylate. The IIP with suitable recognition sites showed a considerably higher response to Pb^{2+} with a wide linear range of 1.0 to 0.08 nM and a detection limit of 0.6 nM (S/N=3).

4. Biomaterials for electrochemical sensing of heavy metal ions

4.1. Enzymes

A variety of enzymes have been reported to be sensitive to specific heavy metal ions as the presence of specific ions can activate or inhibit their activity (Fragoso et al., 2009). Hence, enzymes such as oxidase, peroxidase and urease are commonly used in the design of specific electrochemical sensors for metal ions. For example, based on the inhibition effect of Hg^{2+} to glucose oxidase (GOD), Chey et al. (2012) developed a high specific potentiometric sensor for Hg^{2+} by immobilizing GOD on ZnO nanorods modified electrode. The linear range of the Hg^{2+} inhibition to GOD could be gotten by fixing the concentration of glucose, with a detection limit of Hg^{2+} 0.5 nM, moreover, this sensor had a specificity to Hg^{2+} than the interfering metals such as Cu^{2+}, Zn^{2+}, Fe^{2+} and Co^{2+}. Although the enzyme-based ion sensors offer high specificity, they suffer from the rigorous fabrication conditions and poor stability and reproducibility, which limit their application.

4.2. Amino acids, peptides, proteins and cells

Due to the presence of sulfur, nitrogen and/or oxygen atoms, amino acids, peptides, proteins and cells can be recognized by heavy metal ions via the cooperative metal–ligand interaction and have been used in the detection of heavy metal ions (Shao et al., 2006). For example, a mercury sensor has been designed by incorporating amino acids capped AuNPs in the mixture of carbon paste and ionic liquid, which shows a detection limit of 2.3 nM (S/N=3) (Safavi and Farjami, 2011). Some plant peptides such as phytochelatins and cysteine-rich peptides have been used in the detoxification of excess metals (Chow and Gooding, 2006; Flavel et al., 2011; Lin et al., 2009; Viguier et al., 2011). These peptides are potential modification materials for sensitive detection of heavy metal ions (Changela et al., 2003; Nagaoka et al., 1999). Antibodies as special proteins can specifically bind metal ions and metal-chelate complexes, thus they have been used for detection of heavy metal ions (Wylie et al., 1992). Some microbial sensors have also been prepared for multi-detection of heavy metals (Yang et al., 2012). The *Phormidium.* sp. based microbial sensor shows a low detection limit of 25 nM and a wide linear range from 50 nM to 20 μM for Pb^{2+} (Yüce et al., 2010).

4.3. Functional nucleic acids

As some heavy metal ions can form complexes with certain nucleic acid bases and structures (Clever et al., 2007), functional nucleic acid (FNA) is recently developed for the fabrication of specific sensors for heavy metal ions (Li et al., 2010a, 2014; Wang et al., 2010). The nucleic acid has high chemical and thermal stability and good variation, thus FNAs-based sensors are easier to fabricate and sense a broad range of metal ions. In this part, three different detection strategies for heavy metals with FNAs are summarized.

4.3.1. T–Hg^{2+}–T coordination based sensors

Since Hg^{2+} can interact specifically with thymine bases (T) to form stable T–Hg^{2+}–T biomimetic structure, which is even more

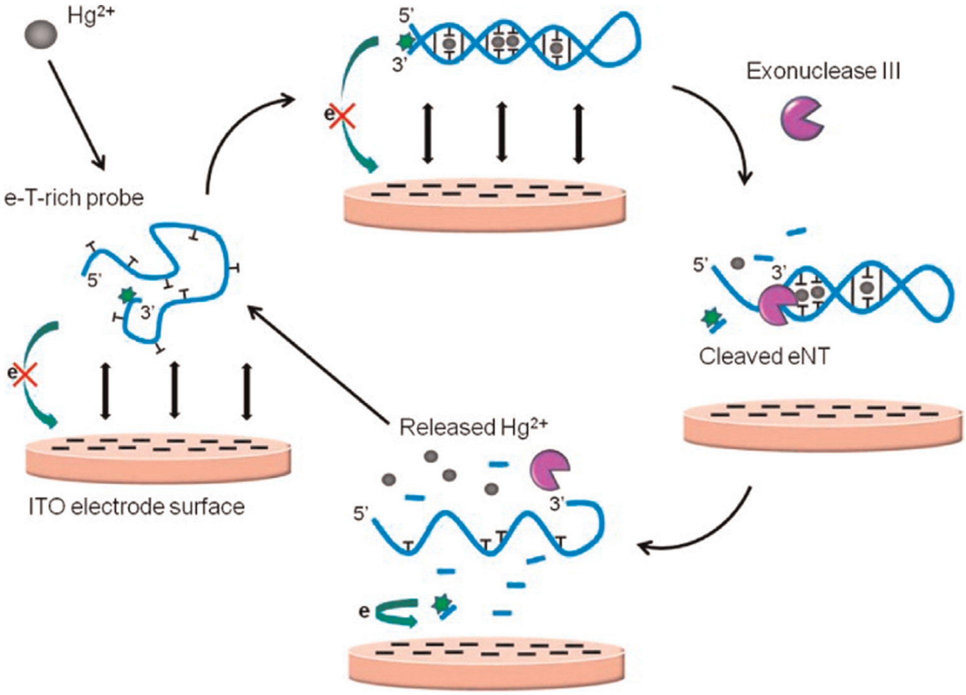

Fig. 7. Illustration of Hg^{2+}-triggered digestion of e-T-rich probe by Exo III monitored with electrochemical monitoring protocol (reproduced from Xuan et al. (2013) by permission of the American Chemical Society).

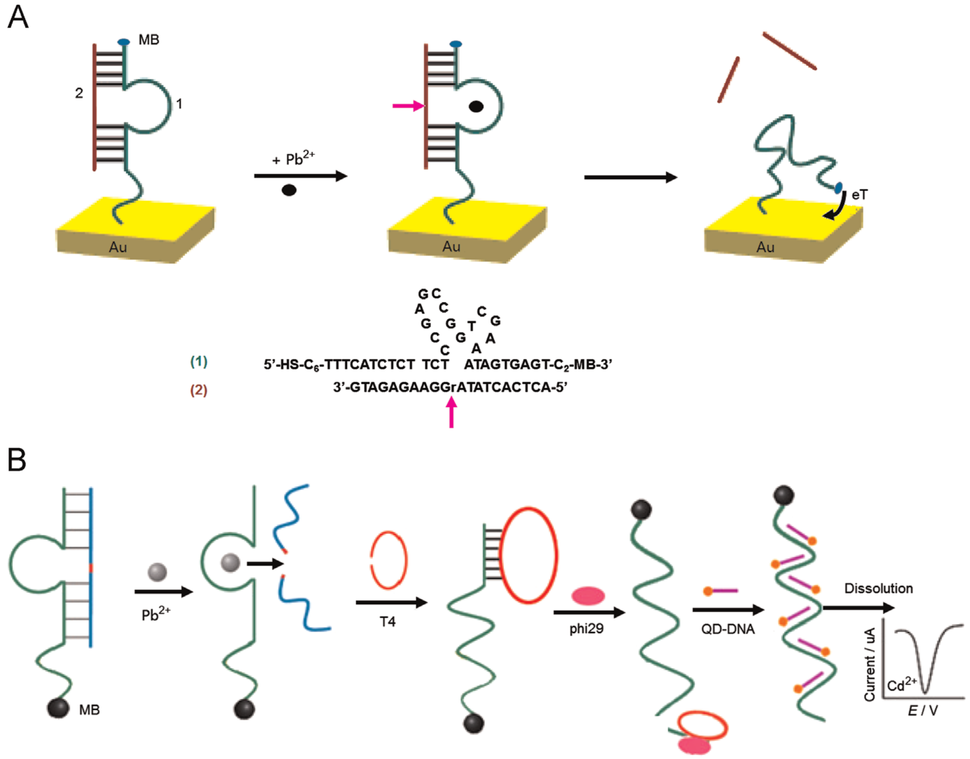

Fig. 8. (A) Schematic illustration of DNAzyme-based electrochemical sensor (reproduced from Xiao et al. (2007) by permission of the American Chemical Society), and (B) principle of the rolling circle amplification-based electrochemical sensing system for Pb^{2+} detection (reproduced from Tang et al. (2013) by permission from Elsevier Science Ltd. UK).

stable than the Watson–Crick adenine–thymine pair (Ono and Togashi, 2004), various electrochemical Hg^{2+} sensors based on T-Hg^{2+}-T coordination have been proposed (Bu et al., 2011; Han et al., 2009; Mor-Piperberg et al., 2010; Shi et al., 2014; Tang et al., 2012; Wu et al., 2010; Xuan et al., 2013). Zhuang et al. (2013) proposed a simple electrochemical strategy for Hg^{2+} detection based on the Hg^{2+}-induced conformational switch of DNA hairpins, which labeled with Fc redox tag in the middle of the loop. In the assay, the presence of Hg^{2+} induced the conformational change from the sticky end to open the hairpins, resulting in the close of ferrocene tags to the electrode and an increasing redox current. This developed Hg^{2+} sensor was simple and low-cost without the participation of auxiliary materials comparing with other signal-on sensors.

Using the same sensing strategy, Xuan et al. (2013) developed a Hg^{2+} biosensor based on Hg^{2+} intentionally trigger the activity of Exonuclease III (Exo III) toward a designed T-rich DNA oligonucleotide by the conformational change of the probe (Fig. 7). Here a methylene blue (MB) labeled T-rich probe was used. The presence of Hg^{2+} induced the formation of T-Hg^{2+}-T base pairs and folded the linear e-T-rich probe into the hairpin structure, which could be cleaved by Exo III to release of mononucleotides as well as MB tag from the T-rich probe. By detecting the amperometric signal of MB tag, the Hg^{2+} was quantified. This assay could detect Hg^{2+} at the detection limit of 0.2 nM due to the enzymatic based amplification.

Besides, the nanomaterials are also combined with the T-rich probe for the detection of Hg^{2+}. For example, a "turn-on" Hg^{2+} sensor was prepared with AuNPs-functionalized reporter DNA to achieve signal amplification (Kong et al., 2009). In this assay, MB could specifically bind with guanine bases resulting in a significant increase in the electrochemical signal, and a detection limit of 0.5 nM Hg^{2+} was obtained. In addition, Wang et al. (2012) presented an assay for taking advantage of the ultrahigh electron transfer ability of GR and its unique GR/ssDNA π–π interaction. Mercury-specific oligonucleotide (MSO) modified Au electrode could adsorb a large amount of GR in the absence of Hg^{2+}, due to the strong noncovalent binding of GR with nucleobases of ssDNA and resulted in the small charge transfer resistance (R_{ct}). Once Hg^{2+} was added, a large decrease of the R_{ct} could be observed. By analyzing the R_{ct} value, a detection limit of 0.5 nM for Hg^{2+} was obtained.

4.3.2. DNAzyme-based sensors

DNAzymes are impressively stable under ambient and even elevated temperatures. Similar to other bioenzymes, DNAzymes can catalyze specific chemical and biological reactions. Recently, metal ion-dependent DNAzymes such as lead and copper-dependent DNAzymes have been widely used for the detection of metal ions (Chen et al., 2014; Hollenstein et al., 2008; Liu and Lu, 2007; Ocaña et al., 2013; Shen et al., 2008; Tang et al., 2013; Wu et al., 2014). For example, Xiao et al. (2007) develpoed an electrochemical Pb^{2+} sensor based on 8–17 lead-dependent DNAzyme (Fig. 8A). The DNAzyme was immobilized on a gold electrode via a thiol–gold interaction, tethering a redox compound MB in the enzyme strand away from the surface of electrode. When Pb^{2+} was added, the substrate strand was cleaved and released into two fragments, and the released enzyme strand was more flexible and facilitated the transfer electrons between MB and the electrode, producing an electrochemical signal proportional to the concentration of Pb^{2+}. The detection limit for Pb^{2+} was 300 nM. The sensor could be successfully applicable in analysis of soil samples.

Similar to the 8–17 DNAzyme, another Pb^{2+}-dependent DNAzyme (GR-5 DNAzyme) has a higher selectivity for Pb^{2+} over other competing metal ions (Lan et al., 2010). For example, Gao et al. (2013a) reported an ECL lead biosensor based on the GR-5 lead-dependent DNAzyme for lead recognition. In the presence of Pb^{2+}, the substrate was cleaved into two fragments at the scissile

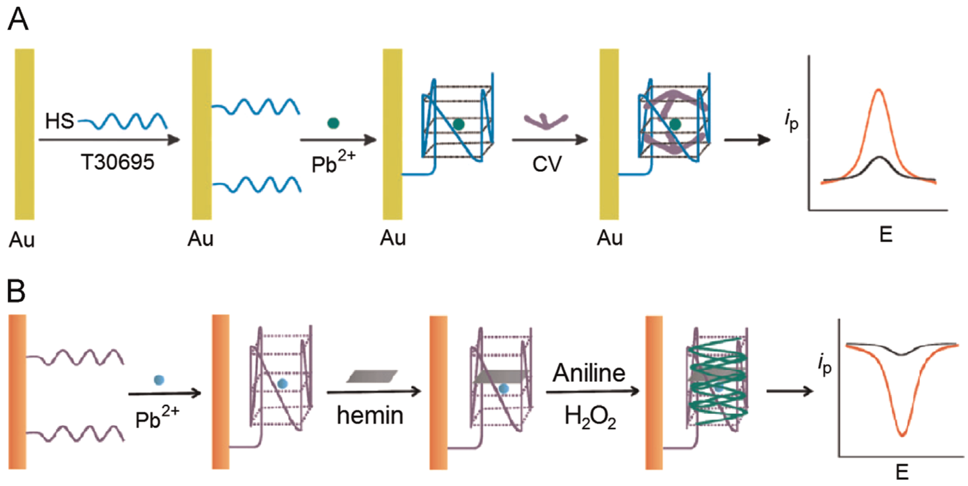

Fig. 9. Schematic illustration of (A) Pb^{2+} detection based on the specific G4–CV interaction (reproduced from Li et al. (2011) by permission of the Royal Society of Chemistry), and (B) versatile sensing platform based on HRP-mimicking DNAzyme-catalyzed template-guided deposition of PANI (reproduced from Li et al. (2013) by permission from Elsevier Science Ltd. UK).

ribo-adenine, leading to the releasing of intercalated ruthenium Tris(1,10-phenanthroline) ($Ru(phen)_3{}^{2+}$) accompanied by a decrease in the intensity of electrochemiluminescence. The biosensor for lead showed an ultra-low limit of detection of 0.9 pM and a wide range from 2 to 1000 pM.

A few DNAzyme based sensors for Cu^{2+} have also been reported. Different from Pb^{2+}-dependent DNAzyme cleaving RNA, the Cu^{2+}-dependent DNAzyeme without the ribo-adenine can be used for the detection of Cu^{2+}. Ocaña et al. (2013) reported a Cu^{2+}-dependent DNAzyme based biosensor for Cu^{2+} detection. In the presence of Cu^{2+}, the DNAzyme reconstituted with Cu^{2+} catalyzed oxidation of ascorbic acid leading to the build-up and adsorption of oxidation products on the electrode surface and produced changes in the interfacial properties of the electrode. The DNAzyme based biosensor combined excellent selectivity against other heavy metal ions with sufficient sensitivity to Cu^{2+} in the range of 6.5–40 μM.

The nanoparticles can also be introduced into the DNAzyme for the detection of heavy metal. Tang et al. (2013) developed a Pb^{2+} biosensor based on DNAzyme, rolling circle amplification (RCA), and CdS QDs modified ssDNA as signaling probe. As shown in Fig. 8B, the DNAzyme was immobilized on the surface of magnetic bead. In the presence of Pb^{2+}, the DNAzyme was activated to cleave the substrate strand into two DNA fragments, and the RCA started when addition of ligase to yield the long ssDNA, repeating sequence units after addition of polymerase and dNTPs. Subsequently, the prepared CdS QD-ssDNA signal probes were hybridized with the long ssDNA product, which resulted in a long DNA duplex with a periodic arrangement of QDs. Therefore, by monitoring the signal change of Cd^{2+} with SWASV, a method for Pb^{2+} determination down to 7.8 pM was achieved.

4.3.3. G-quadruplex-based sensors

DNA G-quadruplexes (G4) processing highly dynamic and polymorphic four-stranded structure can be formed from guanine-rich DNA sequences. Several metals such as K^+, Na^+, and Pb^{2+}, can induce G-rich DNA conformational switch from a random-coil to metal-stabilized G-quadruplex (Li et al., 2010a, 2010b, 2013). According to this DNA structure switching, a label-free electrochemical Pb^{2+} sensor has been developed directly (Lin et al., 2011b). For example, Lin et al. (2011a) proposed an unlabeled immobilized DNA-based sensor for detection of Pb^{2+} by electrochemical impedance spectroscopic with $[Fe(CN)_6]^{4-/3-}$ as redox probe. In the present of Pb^{2+}, G-rich DNA strands formed a G4 structure, leading to the decreased charge transfer resistance, which could be used for Pb^{2+} detection down to 0.5 nM.

Small molecules can be intercalated into the DNA G4 and introduce the signal for the detection of heavy metal ions. For example, Li et al. (2011) developed an electrochemical biosensor based on DNA G4 for Pb^{2+} detection (as schematically shown in Fig. 9A). In the presence of Pb^{2+}, it induced G-rich DNA conformational switch from a random-coil to G4. Crystal violet (CV), as the G4-binding indicator, efficiently intercalated into the formed G4, resulting in a readily measurable “turn–on” electrochemical signal. The result gave a linear correlation to the logarithm of Pb^{2+} concentration over the range 1.0 nM to 1.0 mM with the detection limit of 0.4 nM.

In addition, DNA G4 combined with hemin has been proved to have peroxidase-like activity, and can catalyze the peroxidase reactions, such as Pelossof et al. (2010) and Shen et al. (2010). Based on the catalytic activity, peroxidase-mimicking DNAzyme is also commonly used in electrochemical determination of heavy metal ions. For example, Li et al. (2013) developed an amperometric sensing platform for detection of Pb^{2+} based on horseradish peroxidase (HRP)-mimicking DNAzyme-catalyzed template-guided deposition of polyaniline (PANI) (Fig. 9B). After hemin efficiently intercalated into the Pb^{2+} induced-G4 structure, HRP-mimicking DNAzyme was formed, which could catalyze the oxidation of aniline to PANI with H_2O_2, and produce a readily measurable “turn-on” electrochemical signal. The constructed platform exhibited a good linear response toward Pb^{2+} over a wide range of concentration from 1 nM to 1.0 μM with the detection limit of 0.5 nM.

5. Conclusion and future perspectives

This review summarizes inorganic, organic, and bio-material modified electrodes for electrochemical detection of heavy metal ions. These materials can not only improve the electronic properties and increase the effective electrode surface for transfer of the electrochemical signal, but also product detectable signal for indirect detection of heavy metal ions. Thus the resulting methods possess high sensitivity and good specificity. The synergy of various materials, recognition receptors and electrochemical methods can improve the selectivity, stability and sensitivity, thus promote the development of sensors for heavy metal ions.

Compared to other methods such as MS and AAS, the electrochemical measurements are much cheaper and simpler, and easier for miniaturization, which makes it more suitable for online detection. However, the electrochemical detections often suffer from the drawback of poor reproducibility and stability, and most of the reported works only demonstrate the proof-of-concept of sensors for detection of heavy metal ions in buffer solutions or artificial matrices. This is a considerable problem in mass production and complex systems. Therefore, more easy, cheap and reliable techniques for heavy metal detection devices and systems need to be extensively explored in future. Due to facile miniaturization and automatization of electrochemical techniques for portable applications, these electrochemical sensors can be used not only for environmental monitoring but also in the clinical, safety and security fields.

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