

Review Article

Nanocomposites of Graphene with Ferrocene or Hemin: Preparation and Application in Electrochemical Sensing

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Graphene has sparked tremendous interests across many fields such as biosensors, electrochemical energy storage, and electronics due to its extraordinary physicochemical and structural properties. The redox mediator-functionalized graphene composites may obtain highly electroactive materials with better conductivity, dispersion, and compatibility. Ferrocene and hemin, two iron-organic complexes, are the well-known mediators in view of their various properties, including reversibility, regeneration at low potential, and generation of stable redox states. Recently, it has been demonstrated that the use of ferrocene or hemin coupled with graphene can further improve the electrochemical performances of the developed sensors. In this contribution, we, for the first time, reviewed the preparation and applications of ferrocene/graphene and hemin/graphene nanocomposites in electrochemical sensing.

1. Introduction

Graphene is a single-atom-thick planar sheet of sp²-bonded carbon atoms with exciting properties such as extremely high electronic conductivity and superior mechanical strength [1, 2]. Because of its extraordinary physicochemical and structural properties, this exciting new material has quickly sparked tremendous interests across many fields, including biosensors, electrochemical energy storage, and electronics. With these added advantages, it is desirable to harness the useful properties of graphene and its derivatives in composites through the incorporation with various kinds of functional materials such as inorganic nanostructures, organic crystals, polymers, metal-organic frameworks (MOFs), biomaterials, and carbon nanotubes (CNTs). Properties, preparations, and applications of these functionalized graphene hybrid materials have been summarized in many review papers [3–11]. It is well known that electron mediator is highly conductive molecule, having a readily accessible redox couple and working as the electron transfer mediator to shorten the electron transfer distance between the redox center of analyte and electrode surface. Accordingly, redox mediator may be useful for construction of novel graphene-based nanomaterials. The redox mediator-functionalized graphene composites

may obtain highly electroactive materials with better conductivity, dispersion, and compatibility, which made them highly desirable for effective application in electrochemical sensing. Ferrocene and hemin, two iron-organic complexes, are the well-known mediators in view of their various properties, such as reversibility, regeneration at low potential, and generation of stable redox states. Recently, it has been demonstrated that the use of ferrocene or hemin coupled with graphene can further improve the electrochemical performances of the developed sensors. To the best of our knowledge, there is no review paper focusing on the preparation and application of ferrocene/graphene and hemin/graphene nanocomposites. In this paper, we addressed the preparation and emerging applications of graphene loaded with ferrocene or hemin for electrochemical sensing.

2. Ferrocene/Graphene Nanocomposites

2.1. Preparation and Applications of Ferrocene/Graphene Modified Electrode. The commonly used methods for modification of ferrocene or its derivatives on graphene include π - π stacking interaction, covalent bonding, and physical entrapment. The method based on π - π stacking interaction is an

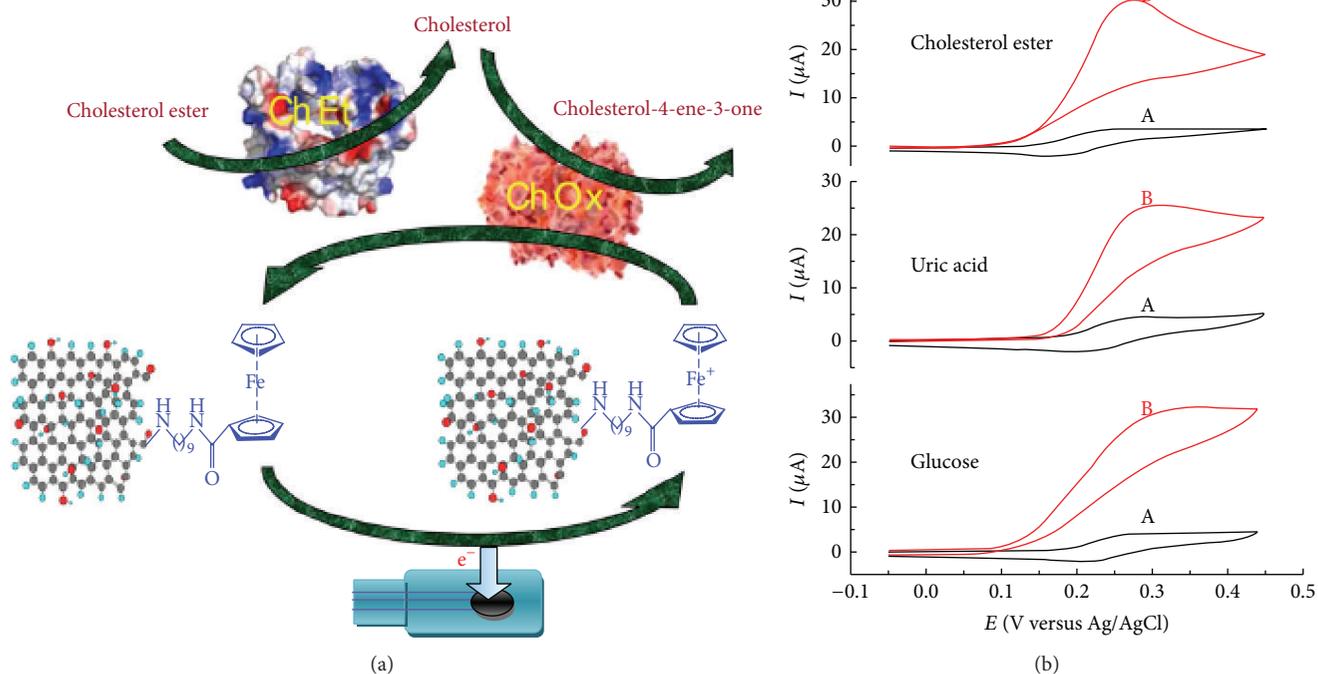


FIGURE 1: (a) Scheme illustrating the biosensing of cholesterol ester mediated by Fc-GO on SPE. (b) Cyclic voltammetric response of the biosensors toward cholesterol ester, uric acid, and glucose in the (A) absence and (B) presence of the respective analytes. (Reprinted with permission from [16]. Copyright 2013 American Chemical Society).

easy means for preparation of ferrocene/graphene nanocomposites [12–14]. By such interaction, the ferrocene/graphene modified graphite electrode has been prepared for the simultaneous electrochemical determination of captopril and hydrochlorothiazide [13]. Furthermore, Deng et al. investigated the electron transfer behaviors of ferrocene/reduced graphene oxide (rGO) on glass carbon electrode and demonstrated its application in detection of H_2O_2 and choline using chitosan for the immobilization of horseradish peroxidase (HRP) and choline oxidase (CHOD) [14]. However, the π - π stacking interaction between the graphene and ferrocene may result in low sensitivity and stability of the biosensor because ferrocene, especially in the oxidized form, can easily diffuse away from the electrode surface into the bulk solution. Therefore, the leakage of electron shuttling ferrocene is a main problem for the modified electrodes. Alternatively, covalently bonded method is a more effective modification means for preparation of ferrocene/graphene nanocomposites [15]. The reported methods for covalent attachment of ferrocene derivatives to graphene include carbodiimide-mediated amine coupling, Schiff's base reaction, and Friedel-Crafts monoacylation. Among them, carbodiimide provides the most popular method for the immobilization of ferrocene derivatives. For example, Dey and Raj demonstrated that ferrocenecarboxylic acid (FcA) could be covalently attached onto the graphene oxide (GO) backbone with diamine sigma spacers of different chain lengths (C3-, C6-, and C9-diamines) and the surface coverage as well as heterogeneous electron transfer rate constant of FcA-GO depended on the length of sigma spacer (Figure 1) [16]. The screen printed

electrodes modified with FcA-GO and the respective redox enzymes allowed for the sensitive detection of cholesterol, uric acid, and glucose. In the process, FcA-GO efficiently mediated the bioelectrocatalytic oxidation of the substrates in the presence of the redox enzymes. Additionally, Liu et al. reported the synthesis of an electroactive graphene composite by covalent immobilization of an amine-terminated ferrocene derivative (4-ferrocenylethyne phenylamine, FEPA) on GO through the interaction between the $-\text{NH}_2$ groups of FEPA and the $-\text{COOH}$ groups of GO. Compared with the alkyl ferrocene derivatives, the "chain-like" FEPA molecule possesses lower resistance and higher electric conductivity. The resulting chitosan/FEPA-GO/GCE showed high sensitivity and selectivity for nitrite detection [17]. Schiff's base reaction is another means for the covalent coupling of ferrocene derivatives to graphene. Typically, ferrocenecarboxaldehyde has been immobilized onto the ethylenediamine- (ED-) functionalized GO through Schiff's base reaction [18, 19]. The resulting ferrocene/graphene nanocomposites showed high electrochemical catalytic ability to the oxidation of H_2O_2 [19] and effective electrochemiluminescence quenching pattern to tris(2,2'-bipyridyl)ruthenium (II) [$\text{Ru}(\text{bpy})_3^{2+}$] [18]. Moreover, Avinash et al. reported the covalent functionalization of GO with ferrocene via the selective Friedel-Crafts monoacylation of ferrocene [20]. This method provided an alternative means for preparation of ferrocene/graphene nanocomposites.

Beside the π - π stacking interaction and covalent bonding, entrapment in ionic liquid (IL), polymers (e.g., nafion, chitosan), or sol-gel matrices provides a unique means

to prepare a three-dimensional network suited for the encapsulation of ferrocene and/or enzymes. IL is a compound consisting entirely of ions that exist in liquid state around room temperature. Recently, IL has been investigated as a biocompatible material for the fabrication of biosensors because of its high chemical and thermal stability, good conductivity, wide electrochemical windows, and good dissolving capability [21]. It has been demonstrated that the hemoglobin/chitosan-IL-ferrocene/graphene modified glassy carbon electrode showed a strong electrocatalytic activity toward the reduction of H_2O_2 due to the favored orientation of hemoglobin in the well-confined surface as well as the high electrical conductivity of the resulting chitosan-IL-ferrocene/graphene inorganic hybrid composite [22]. Moreover, Tajik et al. reported the simultaneous electrocatalytic determination of isoproterenol, acetaminophen, and theophylline using a 1-(4-bromobenzyl)-4-ferrocenyl-1H-[1,2,3]-triazole- (1,4-BBFT-) IL/graphene modified electrode [23].

The grafting of polymers onto graphene is also one of effective methods for the preparation of polymer composites with graphene. Therefore, modification by grafting of polymers onto graphene has been reported by many researchers [24, 25]. For example, nafion's superior properties make it suitable for a broad range of applications; Liu et al. suggested that the presence of nafion and 4-ferrocenylethyne phenylamine (FEPA) in the graphene composite not only provided an excellent environment for dopamine oxidation but also acted as a barrier to prevent ascorbic acid from interfering in the dopamine detection [26]. For low molecular weight mediator compounds, leakage is the main problem in their entrapment in sol-gel matrices. Usually, this limitation can be resolved through direct cross-linking of ferrocene derivatives with polymer, nanoparticles, or high molecular weight compounds before immobilization. For this view, Peng et al. reported the preparation of ferrocene-conjugated ormosil by Schiff's base reaction between the aldehyde group of ferrocenecarboxaldehyde and the amino group of the sol-gel precursor 3-(aminopropyl)triethoxysilane (APTES) [27]. Tetraethoxysilane (TEOS) and the synthesized APTES-ferrocene were then used as the precursors for the sol-gel polymerization. The functional TEOS-APTES-ferrocene composite could effectively prevent the leakage of Fc and showed high stability. As a result, a glucose biosensor was developed by entrapping glucose oxidase (GOD) in the Fc-branched ormosil/chitosan/GO nanocomposites.

Very recently, Fatoni et al. presented a novel molecularly imprinted polymer cryogel biosensor for determination of microalbumin in urine samples by entrapping ferrocene and graphene in the cryogel [28]. Specially, the molecularly imprinted polymer gel was prepared based on the graft copolymerization of acrylamide with $\text{N,N}'$ -methylenebisacrylamide on chitosan using human serum albumin as the template. The subzero polymerization allowed the solvent to form ice crystals and left a macroporous cryogel structure when it was thawed. After removing the template, the specific imprinted surface on cryogel pore walls was used to detect human serum albumin.

2.2. Ferrocene/Graphene/Nanoparticles Hybrid Materials for Electrochemical Sensing. The integration of nanomaterials on graphene potentially paves a new way to enhance their electronic, chemical, and electrochemical properties. Recently, several groups have reported the preparation and application of ferrocene/graphene/nanoparticles hybrid materials. Typically, Han et al. developed a label-free amperometric immunosensor for detection of carcinoembryonic antigen based on chitosan-ferrocene/nano- TiO_2 complex film and AuNPs-graphene nanohybrid. In the work, the AuNPs-graphene nanohybrid was formed on the chitosan-ferrocene/nano- TiO_2 -modified electrode by self-assembly [29]. Liu et al. reported the detection of rutin on ferrocene/AuNPs/graphene sheet-chitosan modified glass carbon electrode [30]. Lately, they presented the fabrication of the nanocomposites of ferrocene thiolate stabilized Fe_3O_4 @Au nanoparticles with graphene sheet/chitosan on a glassy carbon electrode (GCE) surface [31]. The modified electrode allowed for the ultrasensitive and simultaneous detection of ascorbic acid, dopamine, uric acid, and acetaminophen. Using a homogeneous three-component electrodeposition solution containing a ferrocene grafted chitosan hybrid, GOD, and single-walled carbon nanotubes (SWNTs), a homogeneous biocomposite film of ferrocene-chitosan/SWNTs/GOD was immobilized on the surface of 3D graphene foam by one-step electrodeposition [32]. The ferrocene groups grafted on chitosan were stably immobilized on the 3D graphene surface and keep their original electrochemical activity. The SWNTs doped into the ferrocene-chitosan matrix acted as a nanowire to facilitate electron transfer and improved the conductivity of the biocomposite film. Furthermore, a signal amplification detection platform based on the electrochemical rGO-ferrocene hybrid nanocomposite and AuNPs was established for detection of bisphenol A. In the work, the amine-terminated ferrocene derivative was hybridized with GO through covalent coupling reaction. After coupling with HAuCl_4 to simultaneously electrodeposit on the glassy carbon electrodes, the rGO-ferrocene/AuNPs modified electrode was obtained [33].

More interestingly, Wan et al. reported the fabrication of a novel magnetically driven fuel-free graphene carrier loaded with ferrocene (Fc) (Figure 2) [34]. The activation and deactivation of redox-active cargo Fc's redox activity by magnetically driven positioning of the graphene carrier with loaded Fc near and away from the conductive support can be employed for magneto-switchable bioelectrocatalyzed oxidation of glucose by glucose oxidase between active and inactive electrocatalytic states, respectively. The artificially magneto-triggered bioelectrocatalysis and modulation of the electron transfer process of redox biomolecules are extremely important for understanding electron-transport pathways in magneto-triggered biosystems and for mimicking the dynamic properties of magneto-sensitive biochemical reactions in real bioprocesses.

3. Hemin/Graphene Nanocomposites

Hemin is a well-known protoporphyrin found at the active site of heme protein and plays a key role in biochemical

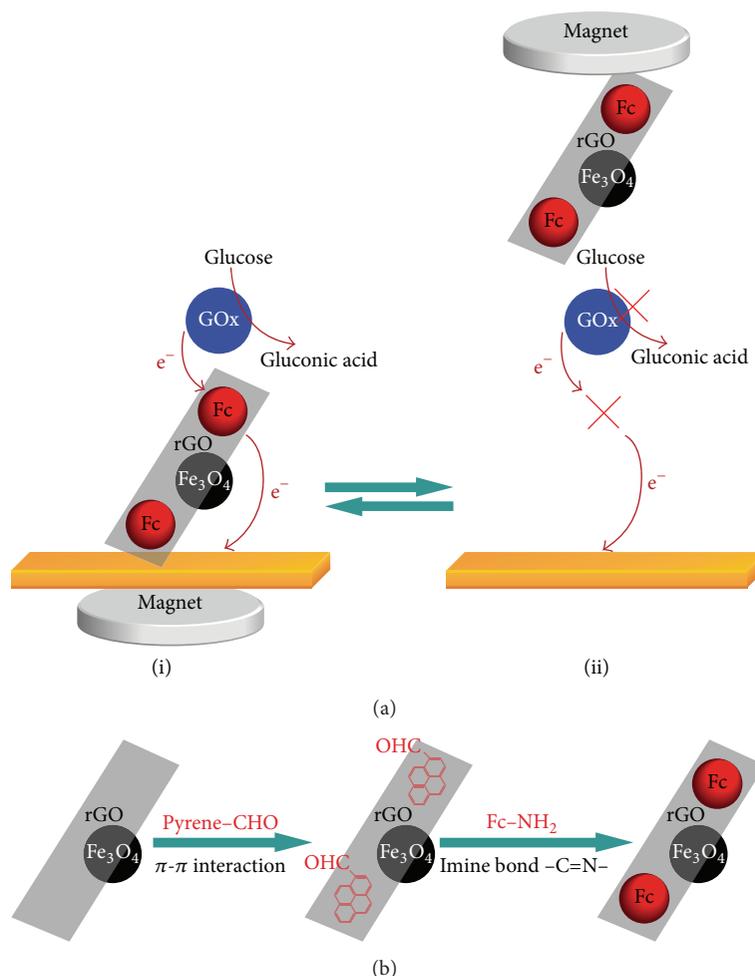


FIGURE 2: (a) Magnetically driven fuel-free graphene carrier with loading of redox-active cargo-Fc working as an electron mediator for mediated bioelectrocatalysis of glucose to gluconic acid by GOx switched between “on” and “off” states under alternate positioning of the graphene carrier with loaded Fc (i) near and (ii) away from the conductive support. (b) The loading of Fc onto the graphene carrier by π - π interaction between Py-CHO and the unoccupied areas of the graphene nanosheet, followed by the formation of imine bond ($-C=N-$) between $-CHO$ group of the Py-CHO modified graphene carrier and the $-NH_2$ group of the Fc- NH_2 . (Reprinted with permission from [34]. Copyright 2014 John Wiley and Sons).

reaction and electron-transport chain [35, 36]. Hemin can be well used as electron media based on the reversible redox of Fe(III)/Fe(II) and hemin-functionalized graphene nanosheets have been shown to exhibit peroxidase activity recently. The preparation and applications of hemin/graphene nanocomposites in electrochemical sensing were also summarized herein.

3.1. Preparation and Applications of Hemin/Graphene Modified Electrode. Among the efforts, the technique of immobilizing hemin on graphene through aromatic π - π interaction was found to be very promising due to its enhanced electron transfer, enhanced electrostatic interaction, excellent electrocatalytic response, peroxidase-like activity, and easy preparation. Typically, conducting interfaces modified with rGO have shown improved electrochemical response for different analytes. The hemin-functionalized rGO hybrid

nanomaterials have been prepared for development of sensitive electrochemical sensors in several groups. For example, Guo et al. reported the first dual biosensor platforms for detection of H₂O₂ and glucose based on rGO/hemin nanosheets [37]. The synergic effect between graphene (high conductivity and surface area) and hemin (excellent catalysis and intrinsic peroxidase-like activity) led to highly efficient electrocatalytic activity for the reduction of H₂O₂ at the rGO/hemin nanosheets modified glassy carbon electrode and exhibited intrinsic peroxidase-like activity that catalyzed H₂O₂ to oxidize 3,3',5,5'-tetramethylbenzidine (TMB) to produce a blue color reaction. Also, Zhang et al. presented the electrogenerated chemiluminescence biosensors for the determination of cholesterol by modifying cholesterol oxidase (ChOx) on the rGO/hemin nanosheets [38, 39]. In above works, rGO was prepared by the chemical reduction of GO with hydrazine. Chemical reduction of GO with NaBH₄,

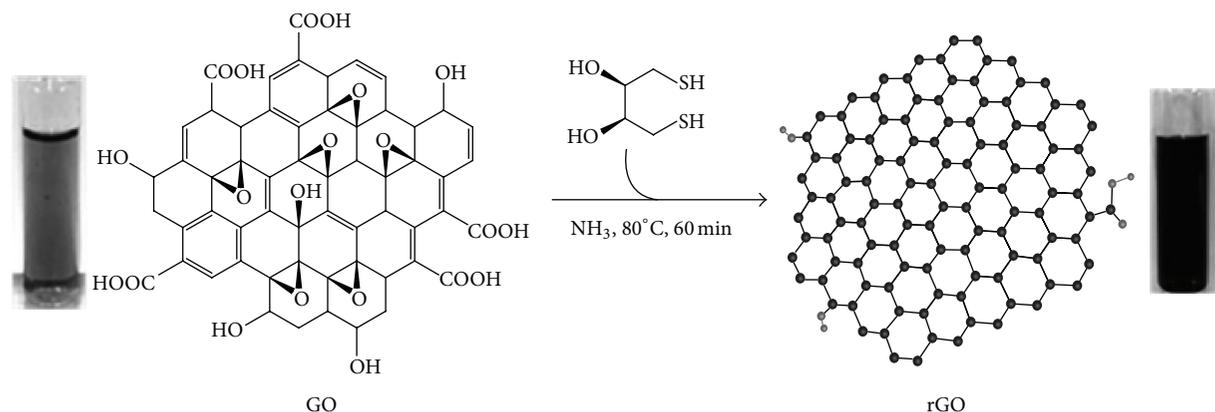


FIGURE 3: Schematic representation of the synthesis of rGO by the reduction using DTT. (Reprinted with permission from [40]. Copyright 2012 John Wiley and Sons).

hydrazine, hydroquinone, dimethyl hydrazine, and Fe/HCl has marked an impact on the generation of copious quantity of rGO with cost effectiveness. However, great care is essential while using these highly toxic and explosive reducing agents [40]. Moreover, functionalization of graphene with polar molecules imparts the hydrophilicity over hydrophobic effects, thus enhancing its dispersibility in polar solvents. For these views, new reducing reagents or reduction methods have been developed for the preparation of graphene-based nanocomposites [41, 42]. Typically, dithiothreitol is a remarkably strong reducing agent with redox potential of -0.33 V at pH 7; Vernekar et al. reported the reduction of GO using dithiothreitol as the reducing agent. The noncovalent functionalization of rGO with hemin resulted in hemin/rGO hybrid material that exhibited a remarkable antioxidant activity for reduction of peroxynitrite (Figure 3) [40]. It has also been demonstrated that GO can be easily reduced using aromatic organic molecules under mild conditions. Oprea et al. found that hemin allowed for the simultaneous reduction of and incorporation into GO nanosheets and that the resulting rGO/hemin showed high peroxynitrite activity [43]. Tang et al. reported a photopolymerization method to prepare rGO/bovine serum albumin (BSA) cross-linked polymer hydrogel/hemin nanocomposites [44]. The GO nanosheets were adsorbed and reduced in situ during the irradiation. The formation of rGO during the UV irradiation and polymerization is mainly contributed to the tyrosine residues of BSA. The large-scale synthesis of ternary nanocomposites of hemin-rGO/poly(3,4-ethylenedioxythiophene) was achieved via a microwave-assisted method [45], in which poly(3,4-ethylenedioxythiophene) was induced with hemin and polymerized with GO and GO was partially reduced. The method did not require the additional oxidant for polymerization and reducing reagents for reduction of GO. The synthesized nanocomposites also exhibited good biocompatibility, fast redox property, and remarkable electrocatalysis towards the reduction of H_2O_2 . Moreover, a hydrothermal method was reported by Wei et al. as a safe and green chemistry route for the reduction of GO. The prepared rGO/hemin nanosheets were used for the electrochemical detection of L-tyrosine [42].

3.2. Hemin/Graphene/Nanoparticles Hybrid Materials for Electrochemical Sensing. Recently, hemin/graphene/nanoparticles hybrid materials have also been used in several sensing and catalytic applications with encouraging results [46, 47]. For example, AuNPs have a large surface area and good conductivity and enable the loading of a large amount of hemin-rGO and the promotion of electron transfer; the layer-by-layer hemin-rGO/AuNPs structure significantly improved the electrocatalytic activity and the electrochemical stability for the determination of H_2O_2 with a detection limit of $0.11 \mu\text{M}$ (Figure 4) [46]. At the same time, Zhang et al. reported a simple wet-chemical strategy for synthesizing hemin/GO/carbon nanotubes nanocomposites through the π - π interactions [47]. The hybrid materials were used to construct a novel dual sensor for the determination of H_2O_2 and the simultaneous determination of ascorbic acid, dopamine, uric acid, and tryptophan. The success of these initial efforts provides good motivation for further manipulation of hemin/graphene/nanoparticles hybrid materials to optimize sensing and catalytic efficiencies.

3.3. Hemin-Loaded Graphene as the Signal Label. It is well known that hemin can be applied in development of electrochemical biosensors as a mimic peroxidase. However, because of the oxidative destruction and the self-aggregation of hemin to form catalytically inactive species, hemin in aqueous solution usually shows low catalytic activity [48]. Recently, graphene and G-quadruplex DNA oligomers have been considered as the successful carriers of hemin for the preparation of electrochemical sensors [49, 50]. The hemin/graphene nanocomposites have also been utilized as the signal labels for electrochemical biosensing typically in a "sandwich-like" format. For example, Zhou et al. developed an electrochemical microRNAs biosensor with carboxylic graphene-hemin hybrid nanosheets as the labels, in which the nanosheets labeled with detection probe DNA for molecular recognition catalyzed the oxidation reaction of hydroquinone in the presence of H_2O_2 due to the intrinsic peroxidase-like activity of hemin on the carboxylic graphene surface [51]. Li et al. reported the amperometric detection of *Escherichia*

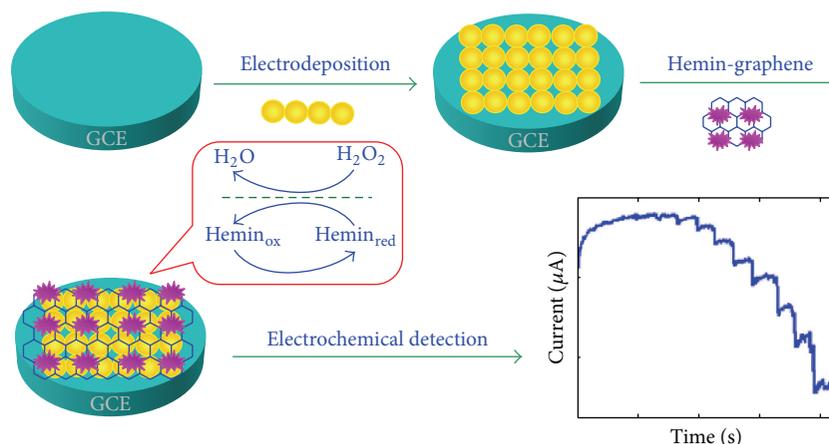


FIGURE 4: Preparation of the H-GNs/AuNP/GCE biosensor for the analysis of hydrogen peroxide followed by the electrochemical detection process and the output. (Reprinted with permission from [46]. Copyright 2013 Elsevier).

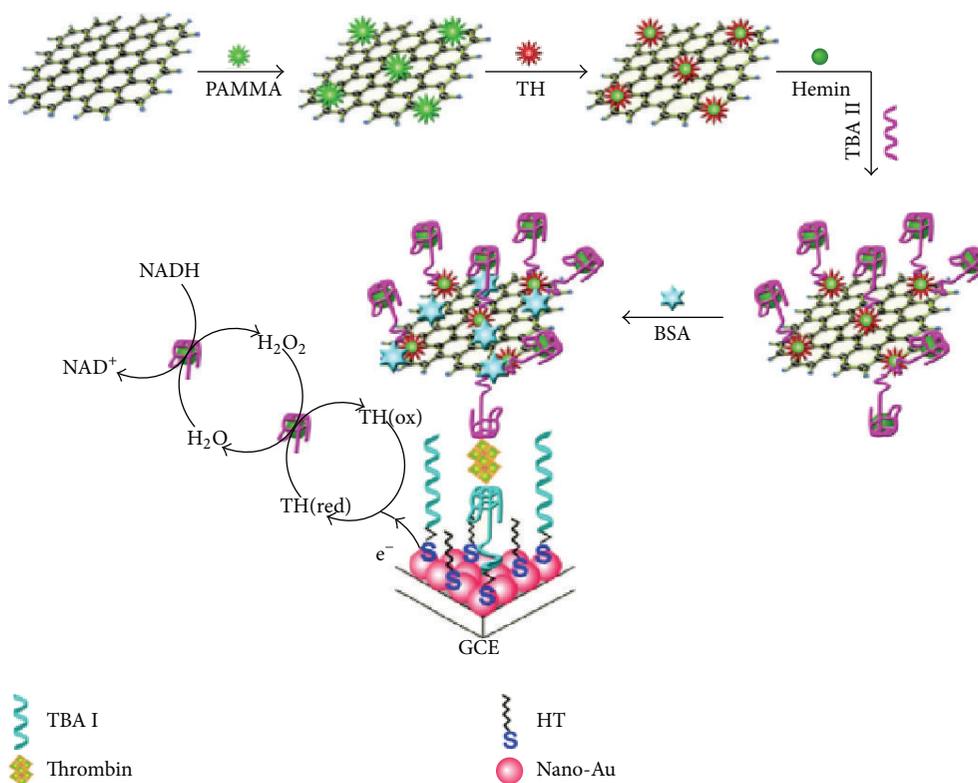


FIGURE 5: Schematic illustration of the pseudobiozyme aptasensor with PAMMA-rGO as nanocarrier and hemin/G-quadruplex as NADH oxidase and HRP-mimicking DNAzyme. (Reprinted with permission from [53]. Copyright 2013 Elsevier).

coli O157:H7 with the signal amplification of graphene-based nanosheets. The nanocomposites were prepared by electrostatic adsorption of thionine and AuNPs-coated SiO₂ on GO, followed by assembly of signal DNA and G-quadruplex to form the hemin/G-quadruplex structure as HRP-mimicking DNAzyme [52]. Furthermore, as HRP-mimicking DNAzyme, the hemin/G-quadruplex structure can act as NADH oxidase simultaneously. For this consideration, Yuan's group developed three types of electrochemical biosensors for thrombin detection using the signal tags of dendrimer-rGO modified

with thionine and hemin/G-quadruplex [53], AuNPs-rGO modified with alcohol dehydrogenase (ADH) and hemin/G-quadruplex [54], and rGO-Pd nanoparticles composites modified with ADH and hemin/G-quadruplex [55], respectively. As shown in Figure 5, the thionine- (TH-) conjugated hemin/G-quadruplex-polyamidoamine- (PAMAM-) rGO was captured on electrode surface. In the presence of NADH, the hemin/G-quadruplex on electrode surface firstly acted as NADH oxidase, facilitating the oxidation of NADH to NAD⁺ with the concomitant local formation of H₂O₂ in

the presence of O₂. Simultaneously, the hemin/G-quadruplex acted as an HRP-mimicking DNAzyme that quickly biocatalyzed the reduction of produced H₂O₂ with dramatic improvement of the oxidation-reduction reaction of the TH mediator, thus leading to an increase in the redox current of TH.

4. Conclusions and Outlook

Recently, the application of ferrocene/graphene and hemin/graphene nanocomposites in electrochemical sensing is an important aspect of the graphene “gold rush.” We, for the first time, reviewed the preparation and application of these nanocomposites in electrochemical sensing. For modification of ferrocene or its derivatives on graphene, π - π stacking interaction, covalent bonding, and physical entrapment ionic liquid, polymers or sol-gel matrices are the commonly used strategies. Among them, covalent bonding is still the most popular method for the immobilization of ferrocene derivatives because it prevents effectively the leakage of electron shuttling ferrocene from electrode surface, thus enhancing the stability and sensitivity of the sensors. Overall, the ferrocene-functionalized graphene nanocomposites acting as the electrode materials have been used for the detection of clinical analytes (e.g., thrombin, cholesterol, uric acid, glucose, ascorbic acid, dopamine, hydrogen peroxide, and choline), drugs (e.g., acetaminophen, theophylline), and environmental pollutants like nitrite and dihydroxybenzene isomers. In the detection system, ferrocene could be regenerated by enzymes or different analytes after its electrooxidation. For grafting of hemin onto graphene, π - π stacking interaction is the most popular method. Additionally, G-quadruplex DNA oligomers have been considered recently as the successful carriers for hemin to form mimic peroxidases. Hemin or hemin/G-quadruplex functionalized graphene nanocomposites act as HRP-mimicking DNAzyme in the detection system. Hemin/graphene and hemin/G-quadruplex/graphene nanocomposites have been used not only as the electrode materials to enhance the biocompatibility, electrocatalysis, and redox property of electrode but also as the signal tags for output. Moreover, the success of the initial efforts on preparation of graphene hybrid materials provides good motivation for further manipulation of ferrocene- and hemin-functionalized graphene/nanoparticles nanocomposites to improve sensing and catalytic efficiencies. We believe that this work would be valuable for the designing of graphene-based new types of electrochemical sensors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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