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Liquid coplanar-gate organic/graphene hybrid electronics for label-free detection of single and double-stranded DNA molecules

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ABSTRACT

The label-free detection of DNA with simple device structure and materials helps rapid and effective diagnosis of various diseases. In this study, liquid coplanar-gate graphene field-effect transistors (GFETs) were employed to detect and further distinguish between single-stranded (SS) and double-stranded (DS) DNA molecules. Use of coplanar-gate structure simplified the fabrication steps for GFETs. The liquid coplanar-gate GFETs exhibited higher sensitivity for DNA detection compared to conventional bottom-gate GFETs because they have liquid dielectric layer that was preferred by aqueous DNA. The immobilization of 1-pyrenebutanoic acid succinimidyl ester (PASE) onto graphene surface via π-π interaction further enhanced the DNA sensing performances of GFETs. The base parts of the SS DNA molecules can be covalently linked to the succinimidyl ester group in PASE/graphene, thereby leading to n-doping of graphene by action of lone-pair electrons from nitrogen atoms in the base parts. On the other hand, the negatively charged phosphate groups of the DS DNA molecules exposed to graphene surface induced p-doping of graphene. Accordingly, it was possible to distinguish the single and double-stranded DNA molecules by electrical signals. The combined use of liquid coplanar-system and surface modification of graphene with PASE could decrease the detection limit of DNA molecules to 1 nM. The liquid coplanar-gate organic/graphene hybrid electronics platform developed here will allow rapid and convenient label-free detection of single and double stranded DNA molecules.

1. Introduction

Graphene has received much attention for its use in biosensors because of several merits, such as large surface area, ease of surface modification for various target molecules, and/or biocompatibility with reduced toxicity [1–3]. In addition, its extremely high charge carrier mobility makes electrical differences even more noticeable, which is beneficial for rapid detection of biomolecules [2]. In particular, graphene field-effect transistors (GFETs) can detect biomolecules with high sensitivity when sophisticately controlling the presumed interactions between graphene and biomolecules. Typically, the contact of biomolecules with graphene surface leads to the doping of graphene and scattering of charge carriers, thereby changes in the Dirac point voltage, and/or source-drain current. GFETs have been employed to quantitatively analyze proteins [4], virus [5], and DNA [6] molecules, and they showed more sensitive performances than traditional analytical methods such as fluorescence spectroscopy and electrophoresis.

The detection of DNA, among various biological molecules, is often the key step for diagnosis of genetic and infectious diseases. DNA sequencing or polymerase chain reaction (PCR) and the following imaging of PCR products are mostly applied for DNA detection. These conventional methods require complicated equipments and pre-defined labeling molecules or probes such as DNA primers and cost much time and labor. If novel label-free simple methods are developed, they will facilitate diagnosis of infectious diseases involving unknown pathogens, in particular, for which pre-defined labeling or probe molecules are not

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available. For this reason, direct detection methods that involve defining the states of binding and orientations of DNA on certain substrates without need of labels, will be useful. Liquid-gate GFETs are regarded as promising methods to achieve this detection goal. Because DNA molecules need aqueous environment to maintain their natural structures and properties, the DNA detection systems should work in wet conditions [7]. Thus, liquid-gate GFETs are advantageous for DNA detection. In conventional liquid-gated GFETs, however, an additional fabrication step is necessary for the formation of gate electrode onto DNA solution [8]. Note that the gate electrode is located in different planes to the source/drain electrodes. In this regard, the coplanar gate method, where the source, drain, and gate electrodes are located in the same plane, can reduce fabrication steps by simultaneously depositing source, drain, and gate electrodes with a single patterning process [9–11].

Defined states of binding and orientation of DNA molecules on the surface of graphene as substrate for sensing will help us to get consistent signals from samples of interest. These favored states can be achieved by adopting the surface chemistry of graphene. Although modification of graphene accompanying the covalent bond can provide functional groups with the graphene surface, but the carrier mobility of GFETs is usually decreased by the defects occurring during the functionalization process, which may eventually lower the performance of sensor. Thus, methods to anchor binding molecules to graphene surface for enhancing its affinity to DNA without causing significant levels of defects are needed [7,12]. One of the example molecules is a 1-pyrenebutanoic acid succinimidyl ester (PASE), where the pyrene group on one side binds to graphene via π-π interaction, and succinimidyl group on the other side covalently binds with amine group of nucleobase (except thymine) in DNA [13]. In this study, we used PASE to enhance the electrical response of graphene to DNA. Single-stranded (SS) and Double-stranded (DS) DNA oligomers (19-mers) were used to simply model the interactions between DNA molecules and graphene. Large-area/high-quality graphene was synthesized with a chemical vapor deposition (CVD) method, and a polymer-supported method was employed to transfer CVD-grown graphene to target silicon substrates. We examined the effects of PASE treatment on the sensing properties for SS versus DS DNA molecules. Liquid coplanar-gate organic/graphene hybrid electronics were fabricated, and their sensing performances were also compared to those of bottom-gate GFETs. Because charge impurities in silicon wafer typically lead to p-doping of graphene, ultrathin polymer brush layer was pre-deposited on silicon wafer, before the transfer of CVD-grown graphene [14–16]. The detection mechanism to distinguish SS versus DS DNA molecules with organic/graphene hybrid electronics was also proposed.

2. Experimental

Graphene was synthesized on Cu foil by a chemical vapor deposition (CVD) method, as reported previously. Silicon wafer with 300 nm thickness of thermally grown SiO_2 purchased from Fine Science was cleaned with acetone and isopropanol. The substrate was treated with UV/ozone for 30 min to create hydroxyl functional groups in SiO_2. Dimethylchlorosilane-terminated polystyrene (PS brush, Mn = 8 kDa) was purchased from Polymer Source. The 0.3 wt % PS brush solution in toluene was spin-casted on the hydroxyl terminated SiO_2/Si with a spin speed of 1100 rpm for 30 s, then followed by baking at 130 ^{O}C for 1 h to allow the reaction of PS brush on the hydroxyl groups of the SiO_2 surface by siloxane linkage [17,18]. The substrate was sonicated in toluene for 30 s to remove excess PS brush that had not reacted on the surface of the substrate [18]. All the experiments of PS brush preparation were conducted in the ambient condition. Graphene on Cu foil was transferred onto a target substrate by using a poly(methyl methacrylate) (PMMA) supporting layer. The Cu layer on the back of graphene was etched by floating PMMA/graphene in the 0.1 M ammonium persulfate solution for 2 h. PMMA/graphene was transferred to a distilled water and cleaned for 30 min, and then transferred to PS brush/SiO_2/Si substrate. The PMMA was then removed by immersing the PMMA/graphene/PS brush/SiO_2/Si into acetone for 1 h. The graphene surface was optionally modified with 1-pyrenebutanoic acid succinimidyl ester (PASE from Aldrich) by immersing the sample into its solution (5 mM) in dimethylformamide (DMF) for 2 h. The effects of PASE modification were examined by Raman spectroscopy (Witec alpha 300R). To fabricate graphene transistors, Au source/drain (bottom-gate), source/drain/gate (liquid coplanar-gate) electrodes were thermally evaporated on the graphene through a shadow mask with the channel lengths and widths of (2000 and 1500) μm (bottom-gate), and (500 and 500) μm (liquid coplanar-gate), respectively. SS and DS DNA oligomers (19-mers) were designed and synthesized by Macrogen and their sequences were 5′-TGGCGTTCCTATTGGTTAA-3' (SS) and 5′-TGGCGTTCCTATTGGTTAA-3'/3′-ACCGCAAGGATAACCAATT-5' (DS), respectively. The SS DNA oligomer has a hairpinless structure whereas the DS DNA oligomer exhibits a complimentary structure with base pairing. We predicted the folding free energy of the hairpin structure through vector NTI software. The electrical properties of GFETs were examined by using a semiconductor analyzer (Keithley 4200-SCS) operating in ambient condition.

3. Results and discussion

Fig. 1 illustrates the fabrication process for graphene on PS brush/SiO_2/Si, bottom-gate GFETs, and liquid coplanar-gate GFETs. The detailed steps for the preparation of GFETs with PS-modified silicon substrate are described in the Experimental Section. Surface treatment with PS brush reduces charge impurities on the SiO_2 surface, thereby resulting in an increase of field-effect mobility with minimized doping of graphene. Bottom-gate GFETs were fabricated by depositing Au source/drain electrodes on the top of graphene. Solutions containing DNA molecules were placed on the channel region of GFETs and dried completely in ambient condition (Fig. 1b). Figure S1 in the Supporting Information (SI) shows the transfer curve of the DNA sensor fabricated with the bottom-gate GFETs. Loading of solution containing SS DNA molecules at the concentration of 300 nM resulted in a decrease of current, while the Dirac point voltage did not shift significantly (Figure S1a). On the other hand, 300 nM of DS DNA oligomer solution at the same concentration led to an upward shift of Dirac point (Figure S1b). The resultant p-doping of graphene with DS DNA was reported in several studies [7,19]. However, it was not possible to clearly distinguish SS DNA with DS DNA from the observed shifts of the Dirac point voltage. The DNA molecules were presumed to be in aggregated forms after drying of its solvent. Accordingly, the interactions between the graphene and dried DNA cannot be sufficient. Also, the large range of the sweeping gate voltage (from −10 to 15 V) was problematic in bottom-gate FETs. Thus, liquid-gate FETs that can work in wet condition and low gate voltage were fabricated as schematically shown in Fig. 1c. Instead of conventional liquid-gate FETs with floating gate, we used coplanar gate FETs where source, drain, and gate electrodes were placed in the same plane. These coplanar-type FETs are advantageous both for reducing the fabrication process and for integrating other types of devices.

To enhance the interactions between graphene and DNA, graphene surface was treated with PASE. Fig. 2 shows the Raman Spectra from the graphene before and after PASE treatment. Pristine graphene exhibited positions of G-band at 1584 cm^{-1} and 2D-band at 2678 cm^{-1} with no significant level of D-band. The slight p-doping of graphene might be caused by water and/or O_2 molecules in the ambient condition. Even after the immobilization of PASE onto graphene, neither the positions of G and D bands changed, nor their intensity ratio (Table 1). Because π-π interaction between the pyrene groups in PASE and graphene is the main driving force for binding of PASE to graphene, neither new covalent bond nor charge transfer occured [20]. The small peak for D-band in the Raman spectra is due to the formation of defects