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Facile Fabrication of Multi-targeted and Stable Biochemical SERS Sensors

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Abstract: The direct transfer of single-crystalline Au nanowires (NWs) onto Au substrates was achieved by a simple attachment and detachment process. In the presence of a lubricant, Au NWs grown vertically on a sapphire substrate were efficiently moved to an Au substrate through van der Waals interactions. We demonstrate that the transferred Au NWs on the Au substrate can act as sensitive, reproducible, and long-term-stable surface-enhanced Raman scattering (SERS) sensors by detecting human α-thrombin as well as Pb^{2+} and Hg^{2+} ions. These three biochemically and/or environmentally important analytes were successfully detected with high sensitivity and selectivity by Au NW-SERS sensors bound by a thrombin-binding aptamer. Furthermore, the as-prepared sensors remained in working order after being stored under ambient conditions at room temperature for 80 days. Because Au NWs can be routinely transferred onto Au substrates and because the resultant Au NW-SERS sensors are highly stable and provide with high sensitivity and reproducibility of detection, these sensors hold potential for practical use in biochemical sensing.

Keywords: gold · nanowires · sensors · surface-enhanced Raman scattering · transfer

Introduction

One-dimensional nanostructures have become the focus of numerous research efforts due to their remarkable chemical and physical properties.[1] In the past decade, they have been employed as promising building blocks for nanoelectronic[2] and optoelectronic devices,[3] biochemical sensors,[4] and energy conversion and harvesting systems.[5] Nanowires (NWs) have been widely used for biochemical sensing because the diameters of NWs are comparable to the size of biological and chemical species. Therefore, NWs can act as excellent signal transducers for such species.[6] Among the various types of NWs, noble-metal NWs exhibit unique optical properties that can be exploited for ultrasensitive detection of biochemical molecules.[4,7] Thus, several noble-metal NW-based sensors have been developed that use optical signals, such as fluorescence,[7b,8] surface-enhanced Raman scattering (SERS),[4] and localized surface plasmon resonance.[9]

SERS is a fascinating phenomenon that substantially increases Raman signals compared to normal Raman signals.[7a,10] This Raman enhancement makes SERS an attractive sensing method with single-molecule-level sensitivity.[11] The use of single-crystalline noble-metal NWs is highly advantageous for the SERS-based detection of biochemical species because their well-defined geometric architecture provides highly reproducible SERS signals.[7a,12] Single-crystalline noble-metal NWs are typically synthesized via bottom-up approaches, and the as-synthesized NWs are randomly oriented or epitaxially aligned on a substrate.[13] Therefore, the transfer of single-crystalline noble-metal NWs onto the desired substrates is critically important in the preparation of SERS-active platforms.[4e] In our previous studies, noble-metal NWs were transferred one by one from the growth substrates to Au substrates using a nanomanipulator to fabricate an efficient SERS-active platform.[4e,14] This method enables the precise control of the NWs and provides a high-quality NW-SERS sensor. However, this method is still time-consuming and has become a bottleneck step for the practical application of NW-SERS sensors. Herein, we report an extremely simple method for transferring single-crystalline Au NWs onto Au substrates for the large-scale fabrication of sensitive, reproducible, and highly stable SERS sensors. Vertically grown Au NWs on a sapphire substrate can be horizontally transferred onto an Au substrate via a simple attachment and detachment process, and the resulting Au NWs on the Au substrate are superb SERS-active platforms. By combining Au NW-SERS sensors with a thrombin-binding aptamer (TBA; 5′-GGTTGGTGTGGTTGG-3′), we successfully detected

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human α-thrombin in a single step with a detection limit of 10 pM, which is one order of magnitude lower than that of a previously reported SERS sensor.[15] In addition, lead ions (Pb^{2+}) and mercury ions (Hg^{2+}) were also detected by Au NW-SERS sensors at concentrations of 10 pM and 10 nM, respectively. More importantly, we demonstrated that the Au NW-SERS sensors still function well 80 days after fabrication. Because the present study illustrates a simple method for the fabrication of sensitive, reproducible, and stable Au NW-SERS sensors, we anticipate that this method and the corresponding Au NW-SERS sensors will find use for the practical sensing of various biological and chemical molecules.

Results and Discussion

Several methods have been used for the transfer and assembly of NWs, including the Langmuir–Blodgett method,[16] flow-assisted alignment,[17] the bubble-down technique,[18] electric-field-directed assembly,[19] and the contact-printing method.[20] Among these methods, the contact-printing method is the most suitable for the transfer of NWs from the growth substrates to the desired substrates.[1] We adopted this method to transfer the vertically grown single-crystalline Au NWs onto Au substrates. In general, the contact-printing method involves the sliding step of a NW-grown substrate on top of a receiver substrate for the application of shear force.[1,20] However, we attempted to move the Au NWs onto the Au substrates using only a simple attachment and detachment process without the sliding step because this step can induce scratches on the surfaces of Au substrates, which impedes the construction of SERS-active platforms.

Figure 1a shows a schematic of the transfer of Au NWs onto an Au substrate via a simple attachment and detachment process. Au NWs with a diameter of approximately 150 nm were vertically grown on a sapphire substrate using the vapor-phase transport method (Figure 1b).[13b] The as-synthesized Au NWs are single-crystalline without twins and have atomically smooth surfaces.[13b] To transfer the Au NWs onto an Au substrate, we flipped the NW-grown sapphire substrate onto an Au substrate using a lubricant and detached it (Figure S1 in the Supporting Information). During this process, the Au NWs were bent and broken by the application of normal force and were transferred from the sapphire substrate to the Au substrate through van der Waals interactions between the Au NWs and the Au substrate. We used a drop of distilled water as a lubricant for the efficient transfer of the Au NWs. The use of a lubricant is highly beneficial to the construction of well-defined NWs on substrate structures because it minimizes the effects of mechanical friction.[1,20a] In the absence of a lubricant, Au NWs embedded into the Au substrate were often observed. However, in the presence of a lubricant, all of the NWs were horizontally transferred onto the Au substrate, thereby providing well-defined SERS-active structures. Figure 1c shows an optical image of the Au NWs after transfer to the Au substrate. The transferred Au NWs are well dispersed, and the surface of the Au substrate is not scratched.

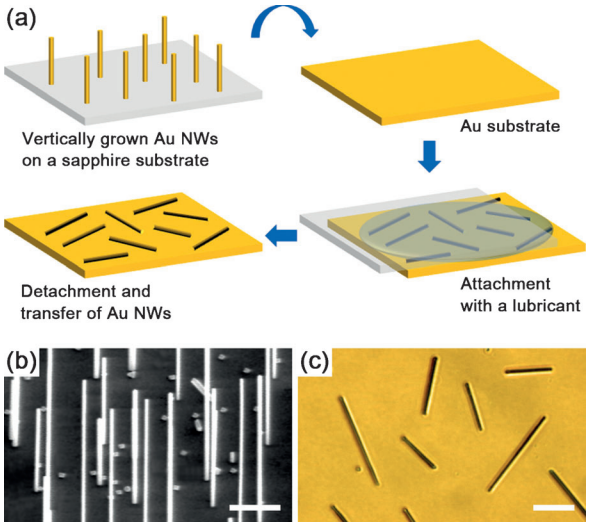

Figure 1. (a) Schematic illustration of the transfer of Au NWs onto an Au substrate by a simple attachment and detachment process. An Au NW-grown sapphire substrate was flipped onto an Au substrate with a lubricant and was subsequently detached. During this process, the Au NWs were bent and broken by the application of normal force and were transferred onto the Au substrate. (b) SEM image of Au NWs vertically grown on a sapphire substrate. Scale bar, 2 μm. (c) Optical image of Au NWs transferred onto an Au substrate. Scale bar, 5 μm.

For the fabrication of Au NW-SERS sensors by this simple NW transfer method, we attached Cy5-labeled TBA to the surface of the Au NWs and then transferred the NWs onto an Au substrate. Because TBA can bind to human α-thrombin with a dissociation constant of 25 nM as well as to Pb^{2+} and Hg^{2+} ions,[15,21] the as-prepared Au NW-SERS sensors can be used for the detection of human α-thrombin, Pb^{2+}, and Hg^{2+}. Cy5 is a well-known Raman reporter for the 633 nm excitation source.[4d] Because Cy5 has an absorption maximum of 647 nm, the 633 nm light can excite the resonant vibration of the molecule, thereby providing strong resonance Raman signals.[4d] First, we tested the reproducibility of the SERS signals from the fabricated sensors. Achieving reproducible SERS signals is the most important task for real-world applications of SERS sensors. Figure 2a shows an optical micrograph of an Au NW-SERS sensor and Figure 2b shows the Raman mapping image of the same sensor. The band intensity at 1580 cm^{-1} was used for Raman mapping. The result clearly shows that the SERS signals for Cy5 were consistently obtained along the whole Au NW, thus indicating the sample uniformity. Figure 2c shows the SERS spectra for Cy5 measured with five different Au NW-SERS sensors, demonstrating the signal reproducibility. All of the spectra show similar band intensities at 1185, 1360, 1485, and 1580 cm^{-1}, which correspond to $\nu(C{-}N)_{stretch}$, $\nu(C{=}C)_{ring}$, $\nu(C{-}C)_{ring}$, and $\nu(C{=}N)_{stretch}$, respectively.[4d] Therefore, the Au NW-SERS sensors fabricated by the simple attachment and detachment method provided highly reproducible

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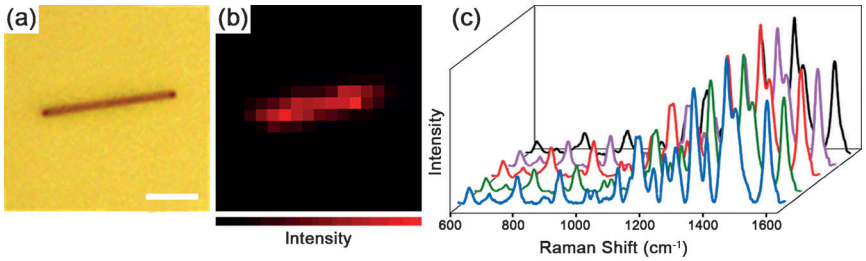

Figure 2. (a) Optical image of an Au NW-SERS sensor. Scale bar, 2 μm. (b) Raman mapping image of the same sensor. The 1580 cm^{-1} band intensity of Cy5 was used for Raman mapping. (c) SERS spectra for Cy5 measured with five different Au NW-SERS sensors. The similar intensity in each spectrum indicates that the Au NW-SERS sensors are highly reproducible.

SERS signals, which suggests that reliable biochemical sensing is feasible with these sensors. Recently, Chang et al. reported the large-scale fabrication of SERS-active Ag NW crossbars by a two-step transversal capillary transfer microprinting approach.[22] Compared to NW crossbars, Au NW-SERS sensors can be constructed rather easily and provide quite reproducible SERS signals along the whole NW.

We attempted to detect human α-thrombin at various concentrations using Au NW-SERS sensors. TBA attached to Au NWs is able to recognize human α-thrombin by inducing a conformational change of the molecule.[15] Therefore, TBA is displaced from the Au NWs, and the SERS signals for Cy5 decrease.[15] Figure 3a shows the whole SERS spectra for Cy5 measured with the Au NW-SERS sensors as the concentrations of human α-thrombin were varied. The SERS signals decreased as the concentration of human α-thrombin increased. For quantitative analysis, the band intensity at 1580 cm^{-1} was selected, and the plot of this band intensity as a function of the concentration of human α-thrombin shows that the Au NW-SERS sensors have a detection limit of 10 pM with a dynamic range from 10 pM to 10 nM (Figure 3b). In comparison with a previously reported SERS-based human α-thrombin sensor,[15] the Au NW-SERS sensor has a 10-fold lower detection limit. In addition, we examined the selectivity of this sensor by using a non-specific binding protein, bovine serum albumin (BSA), instead of human α-thrombin. Figure 3c shows the band intensity at 1580 cm^{-1} as a function of the target molecule. In the presence of 100 nM human α-thrombin, the intensity of the SERS signals was substantially decreased (blue column in Figure 3c). However, in the presence of 1 μM BSA, the intensities of the signals were unchanged (magenta columns in Figure 3c). Based on this result, we confirmed that the change in the SERS signals is dependent on the specific recognition of human α-thrombin.

Because TBA can also bind Pb^{2+} and Hg^{2+} ions,[21] the Au NW-SERS sensors can detect these metal ions without any additional preparation steps. Figure 4a,b show plots of the band intensity at 1580 cm^{-1} as a function of the concentration of Pb^{2+} and Hg^{2+} ions, which verify the metal ion sensing ability of the Au NW-SERS sensors. The detection limits were determined to be 10 pM for Pb^{2+} and 10 nM for Hg^{2+}. For the detection of Pb^{2+} ions, the Au NW-SERS sensor has a highly improved detection limit compared to previous data.[23] For Hg^{2+} sensing, however, the Au NW-SERS sensor exhibits a relatively high detection limit.[4d,24] This reduced sensitivity may be attributed to the low affinity of TBA for Hg^{2+}. According to the US Food and Drug Administration and the US Environmental Protection Agency, the

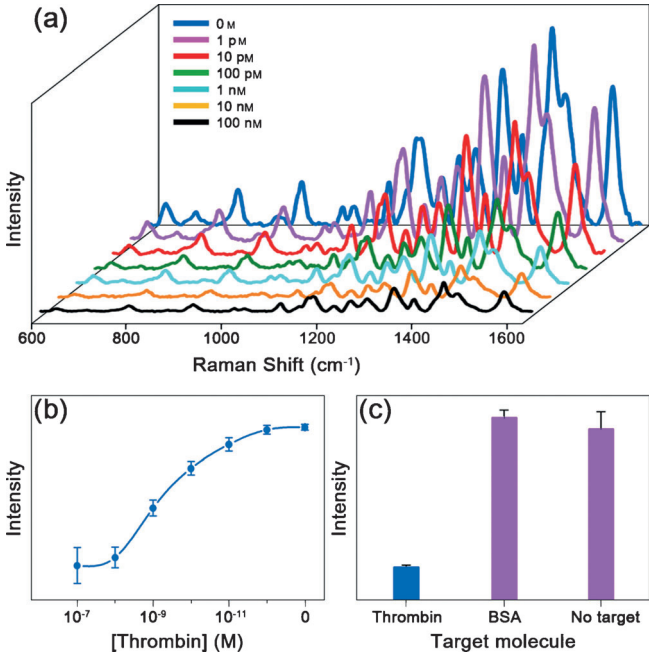

Figure 3. (a) SERS spectra of Cy5 measured by the Au NW-SERS sensors at various concentrations of human α-thrombin. The intensity of Cy5 bands decreases as the concentration of human α-thrombin increases. (b) Plot of the intensity of the band at 1580 cm^{-1} as a function of the concentration of human α-thrombin. The detection limit was estimated to be 10 pM. (c) Plot of the intensity of the band at 1580 cm^{-1} as a function of the target molecule. In the presence of 10 nM human α-thrombin, the intensity of the SERS signals was significantly decreased (blue column). In the presence of 1 μM BSA or in the absence of human α-thrombin, the signals were unchanged (magenta columns). Data represent the mean plus standard deviation from ten measurements.

action level of Pb^{2+} is 2.5 μM in products intended for children, and the maximum permitted level of Hg^{2+} is 10 nM in drinking water.[21] Therefore, we expect that the Au NW-SERS sensors can be used to monitor Pb^{2+} and Hg^{2+} levels in foodstuff and in environmental samples. Finally, the long-term stability of the Au NW-SERS sensors was evaluated. The as-prepared Au NW-SERS sensors were stored under ambient conditions at room temperature for 80 days and were then used to detect human α-thrombin (10 nM), Pb^{2+} (10 nM), and Hg^{2+} (1 μM). As shown in Figure 4c, all of the target molecules were successfully detected by the sensors

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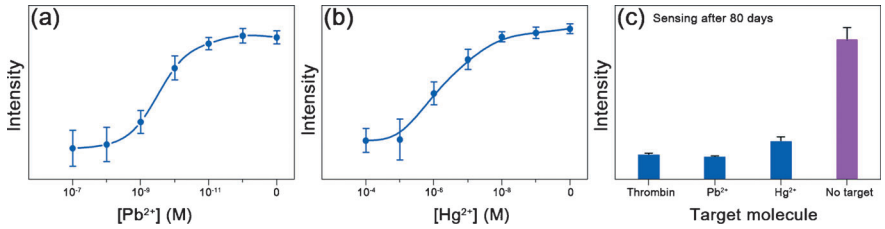

Figure 4. Plot of the intensity of the band at 1580 cm^{-1} as a function of the concentration of Pb^{2+} ions. The detection limit was estimated to be 10 pM. (b) Plot of the intensity of the band at 1580 cm^{-1} as a function of the concentration of Hg^{2+} ions. The detection limit was estimated to be 10 nM. (c) Long-term stability of the fabricated Au NW-SERS sensors. Human α-thrombin as well as Pb^{2+} and Hg^{2+} ions were detected by the Au NW-SERS sensors 80 days after fabrication. Data represent the mean plus standard deviation from ten measurements.

after 80 days. Given that long-term stability is important for the commercial use of biochemical sensors, this result is quite impressive and brings us one step closer to real-world application of SERS sensors.

Conclusions

The current study is important for the following reasons. First, this study provides an extremely simple route for the fabrication of efficient SERS sensors via the transfer of Au NWs onto Au substrates. The vertically grown single-crystalline Au NWs can be moved to Au substrates by an attachment and detachment process in the presence of a lubricant. Second, this study demonstrates that the as-prepared Au NW-SERS sensors are highly reproducible and can be used for the quantitative detection of human α-thrombin as well as Pb^{2+} and Hg^{2+} ions. In particular, these sensors exhibited a low detection limit of 10 pM for human α-thrombin and Pb^{2+}. Third, this study shows that the Au NW-SERS sensors are highly stable for a long period of time. The sensors worked normally after being stored for 80 days under ambient conditions at room temperature. Therefore, we anticipate that routinely constructed Au NW-SERS sensors can be employed for the practical sensing and monitoring of various biological and chemical species.

Experimental Section

Materials

Human α-thrombin, BSA, $Pb(Ac)_2$, $Hg(Ac)_2$, and Au evaporation slugs were purchased from Sigma–Aldrich. The 5'-end thiolated TBA labeled with Cy5 at the 3'end was purchased from Genotech (Daejeon, Korea) and has the sequence of 5′-HS-$(CH_2)_6$-TAAGTT-CATCTCCCCGGTTGGTGTGGTTGGT-Cy5-3′. The TBA was treated with 1 M dithiothreitol (Sigma–Aldrich) to reduce the disulfide bonds and purified by using a NAP-5 column (GE Healthcare).

Synthesis of Single-Crystalline Au NWs

Single-crystalline Au NWs were synthesized on a *c*-cut sapphire substrate in a horizontal quartz tube furnace system by using a previously described vapor transport method.[7a,13b,14] Briefly, the sapphire substrate was placed a few centimeters downstream from an alumina boat filled with an Au slug. Ar gas was flowed at a rate of 100 sccm (sccm = standard cubic centimeter per minute), maintaining the chamber pressure at 1–5 Torr. The high temperature zone of the furnace was heated to 1100 °C. Au NWs were grown on the substrate for a reaction time of 30 min. Au substrates were prepared on Si substrates by electron-beam-assisted deposition of a 10 nm thick film of Cr followed by a 300 nm thick film of Au.

Transfer of Au NWs onto Au Substrates

Au NWs-grown *c*-cut sapphire substrates were flipped over onto Au substrates with a lubricant and detached. As a lubricant, a drop of distilled water was used. We dropped the lubricant onto Au substrates before flipping the Au NWs-grown substrates. After the attachment and detachment process, the remaining water was dried by N_2 gas.

Detection of Target Molecules by using Au NW-SERS Sensors

For the fabrication of Au NW-SERS sensors, as-grown Au NWs were incubated at room temperature overnight in TBA (100 μM) in 1× thrombin-binding buffer (TBB; 140 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 20 mM Tris-acetate, pH 7.4). After incubation, excess TBA was washed off by using 1× TBB. TBA-attached Au NWs were then transferred onto Au substrates by the attachment and detachment process. To detect target molecules, Au NW-SERS sensors were incubated in 1× TBB containing human α-thrombin, Pb^{2+}, or Hg^{2+} for 1 h at room temperature in the dark. After incubation, the sensors were washed with 1× TBB containing 0.1% (w/v) sodium dodecyl sulfate (SDS) several times, rinsed with distilled water, and dried under a N_2 stream. SERS signals of the sensors were measured by using a micro-Raman system. The polarization of the excitation laser was perpendicular to the long axis of Au NWs. For testing the long-term stability, Au NW-SERS sensors were stored under ambient conditions at room temperature for 80 days.

Instrumentation

The micro-Raman system was home-built based on an Olympus BX41 microscope. Radiation of a He-Ne laser (Melles Griot) at 633 nm was used as the excitation source, and the laser was focused on an Au NW through a 100× objective (Numerical aperture = 0.7, Mitutoyo). The polarization direction of the laser was controlled by rotating a half-wave plate. SERS signals were recorded with a thermoelectrically cooled electron multiplying charge coupled device (EMCCD; Andor) mounted on a spectrometer with a 1200 groove per mm grating. Two holographic notch filters were used to remove the 633 nm light. For Raman mapping, a three-dimensional piezoelectric stage (Sigma–Koki) was used by combining with the micro-Raman system.

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