Talanta 132 (2015) 44–51

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Ultrasensitive detection of target analyte-induced aggregation of gold nanoparticles using laser-induced nanoparticle Rayleigh scattering

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ARTICLE INFO

Article history:
Received 18 June 2014
Received in revised form
19 August 2014
Accepted 20 August 2014
Available online 27 August 2014

Keywords:
Laser-induced Rayleigh scattering
Gold nanoparticles
Smart phone
Sensor

ABSTRACT

Detection of salt- and analyte-induced aggregation of gold nanoparticles (AuNPs) mostly relies on costly and bulky analytical instruments. To response this drawback, a portable, miniaturized, sensitive, and cost-effective detection technique is urgently required for rapid field detection and monitoring of target analyte *via* the use of AuNP-based sensor. This study combined a miniaturized spectrometer with a 532-nm laser to develop a laser-induced Rayleigh scattering technique, allowing the sensitive and selective detection of Rayleigh scattering from the aggregated AuNPs. Three AuNP-based sensing systems, including salt-, thiol- and metal ion-induced aggregation of the AuNPs, were performed to examine the sensitivity of laser-induced Rayleigh scattering technique. Salt-, thiol-, and metal ion-promoted NP aggregation were exemplified by the use of aptamer-adsorbed, fluorosurfactant-stabilized, and gallic acid-capped AuNPs for probing K^+, *S*-adenosylhomocysteine hydrolase-induced hydrolysis of *S*-adenosylhomocysteine, and Pb^{2+}, in sequence. Compared to the reported methods for monitoring the aggregated AuNPs, the proposed system provided distinct advantages of sensitivity. Laser-induced Rayleigh scattering technique was improved to be convenient, cheap, and portable by replacing a diode laser and a miniaturized spectrometer with a laser pointer and a smart-phone. Using this smart-phone-based detection platform, we can determine whether or not the Pb^{2+} concentration exceed the maximum allowable level of Pb^{2+} in drinking water.

1. Introduction

Numerous nanomaterials, including magnetic nanoparticles (NPs), metal NPs, quantum dots and carbon-based nanomaterials, have served as signal transducers in a number of reported biosensors because they exhibit high surface area-to-volume ratio, strong signal intensities, and tunable surface chemistry [1–3]. Gold nanoparticles (AuNPs) provide several physical and chemical advantages, making them one of the most popular materials for the fabrication of chemical and biological sensors. First, a number of chemical approaches have been available for a one-pot synthesis of highly stable AuNPs [4]. Second, they possess surface Plasmon resonance (SPR), Rayleigh scattering, electric conductance, redox behavior, and enzyme-mimetic activity [4–8]. Third, they offer extremely large ensemble surface areas with tunable modification options [9]. Fourth, these properties of AuNPs can be readily tuned by varying their size, shape, and the surrounding chemical environment [4]. With these advantages, the binding event between the recognition element and the analyte can cause the change in physicochemical properties of transducer AuNPs, such as the intensity and wavelength of SPR [10], the magnitude of conductivity [11], and the behavior of redox reaction [6]. These changes in turn can produce a detectable response signal for detecting a variety of analyte, such as heavy metal ions, anions, small molecules, proteins, and nucleic acids [4,8,10,12,13].

Because the optical properties of SPR of the AuNPs are strongly dependent on interparticle separation distances and particle size, the current gold standard for detecting the analyte-induced aggregation and growth of the AuNPs is to measure the wavelength and intensity of SPR, respectively. For example, the analyte-stimulated aggregation of the AuNPs drives interparticle surface plasmon coupling, causing a red-shift in the SPR peak [14]. Moreover, the H_2O_2- and dopamine-mediated enlargement of the AuNPs produced an increase in the intensity of SPR peak [15,16]. However, most of these sensors exhibit moderate sensitivity with detection limits for target analyte in the micromolar range. The plasmon scattering intensity of a single 60-nm diameter AuNPs resembles the fluorescence intensity of 10^5 fluorescein molecules. The strong scattering light of the AuNPs arises from the collective oscillation of conducting electrons. Thus, to improve the

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http://dx.doi.org/10.1016/j.talanta.2014.08.055
0039-9140/

sensitivity of AuNP-based colorimetric assays, numerous sensors are established based on the measurement of size-induced change in the maximum peak and intensity of a resonant Raleigh scattering [17]. For example, as compared to the dispersed AuNPs, the analyte-triggered aggregation of the AuNPs can scatter electromagnetic radiation strongly; this change can be monitored using dark-field light scattering [18], dynamic light scattering [19], hyper-Rayleigh scattering [20], and resonance Rayleigh scattering techniques [21]. Dark-field light scattering technique can observe the scattering light of the AuNPs at the single-particle level, but such technique are limited to the detection of relatively large particles (>40 nm) and the quantification of target analyte. Additionally, dynamic light scattering, hyper-Rayleigh scattering, and resonance Rayleigh scattering techniques are rather costly, time-consuming procedure, sophisticated, and non-portable.

Herein, we reported a highly sensitive light-scattering technique for sensing K^+, *S*-adenosylhomocysteine hydrolase (SAHH) activity, and Pb^{2+} based on the fact that salt- thiol-, and metal ion-induced aggregation of the AuNPs greatly enhances light scattering, respectively. The measurement of light scattering is easy to perform using a miniaturized spectrometer as a scattering detector and a 532-nm laser as an excitation light. The integrated scattering spectrum was obtained by placing the detector at right angle to the excitation beam. The proposed method can provide more than 10-fold improvement in limit of detection (LOD) compared to colorimetric assay.

2. Experimental

2.1. Chemicals

S-adenosylhomocysteine (SAH), SAHH (rabbit erythrocytes; 50,000 units/L; MW 240,000), homocysteine (HCys), bovine serum albumin (BSA, from bovine serum), human serum albumin (HSA, from human serum), trypsin (from porcine pancreas), lysozyme (from human milk), thrombin (from bovine plasma), myoglobin (from equine heart), cytochrome c (from bovine heart), hemoglobin (from bovine blood), fluorosurfactant (FSN), trisodium citrate, $HAuCl_4$, gallic acid, NaH_2PO_4, Na_2HPO_4, NaCl, $NaClO_4$, $MgCl_2$, $FeCl_3$, NH_4HCO_3, $Cd(ClO_4)_2$, NaOH, $Pb(NO_3)_2$, and $HgCl_2$ were obtained from Sigma-Aldrich (St. Louis, MO). $FeCl_2$, $CuCl_2$, $SrCl_2$, LiCl, KCl, $CoCl_2$, $NiCl_2$, $CaCl_2$, $MnCl_2$, $BaCl_2$, $ZnCl_2$ were obtained from Acros Organics (Geel, Belgium). The molecular formula of FSN is $F(CF_2CF_2)_{3-8}CH_2CH_2O(CH_2CH_2O)_xH$. Gold nanoparticles (15, 30, 50 nm) were purchased from Ted Pella Inc. (Redding, California). DNA sample (K^+ aptamer, 5′-GGG TTA GGG TTA GGG TTA GGG-3′) was synthesized from GenScript Corporation (Taipei, Taiwan). Isotonic phosphate-buffered saline ($1\times$ PBS; pH 7.4) was prepared by dissolving $Na_2HPO_4{\cdot}2H_2O$ (22.05 g), $NaH_2PO_4{\cdot}H_2O$ (2.07 g), and NaCl (4.5 g) in H_2O (1.0 L). Water used in all of the experiments was doubly distilled and purified by a Milli-Q system (Millipore, Milford, MA, USA).

2.2. Synthesis of 4 nm-sized AuNPs

The preparation of AuNPs was conducted by adding $NaBH_4$ (0.1 M, 1.5 mL) to a solution (50 mL) containing 250 μM $HAuCl_4$ and 250 μM trisodium citrate under vigorous stirring. The image of transmission electron microscopy (Tecnai 20 G2 S-Twin, Philips/FEI, Hillsboro, Oregon) demonstrated the size of the as-prepared AuNPs (Fig. S1, Supplementary information).

2.3. Apparatus

A diode-pumped solid state continuous laser (Labguide Co., Ltd) with a wavelength of 532 nm was used as an excitation light source when its output power was 5 mW. A miniaturized QE65000 Scientific-grade Spectrometer (Ocean Optics, Inc.) was used for collecting the scattering of the AuNPs. An Ocean Optics CUV-ALL-UV four-way cuvette holder (Ocean Optics, Inc.) equipped with fiber-optic couplings at each of four quartz *f*/2 collimating lenses was incorporated to a 1000 μm illumination fiber and a 1000 μm read fiber. An illumination fiber brings the excitation beam to a cuvette, while a read fiber transports the scattering signal back to Ocean Optics QE65000 spectrometer. The scattering spectrum was recorded using Ocean optics SpectraSuite spectroscopy software with 100 ms integration time. To reduce the cost of instrumentation and toward more portable system, a battery-operated green laser point (532 nm) and a smart-phone (Samsung, Galaxy SIII) were used in place of a diode-pumped solid state continuous laser and a Ocean Optics QE65000 spectrometer, respectively.

2.4. Sensing of potassium ion

Citrate-capped AuNPs (15 nm; 1.5 nM, 10 mL) were modified with K^+ aptamer (100 μM, 100 μL) for 2 h at ambient temperature. Metal ions (4–5000 μM) reacted with aptamer-modified AuNPs (0.75 nM) for 5 min at ambient temperature. The resulting solutions were incubated with $0.1\times$ PBS solution for 5 min at ambient temperature. The scattering spectra were collected using the proposed detection system.

2.5. Sensing of SAHH activity

Citrate-capped AuNPs (15 nm; 2.5 nM, 60 mL) were modified with FSN (10% w/v, 240 μL). FSN-stabilized AuNPs were stored at 4 °C until further use. Proteins (0–100 units/L, 100 μL) reacted with SAH (100 μM, 100 μL) in 50 mM phosphate buffer (pH 7.2) at 37 °C for 20 min. We incubated the resulting solutions (200 μL) with a solution (800 μL) containing FSN-AuNPs (0.1 nM) and phosphate buffer (100 mM, pH 5) for 10 min and recorded their scattering spectra.

2.6. Sensing of lead ion

The pH of $HAuCl_4$ was adjusted to 11.1 by adding 100 μL of 0.5 M NaOH. A solution of gallic acid was heated to 50 °C. Subsequently, gallic acid (0.1 mL, 38.8 mM) was added slowly to $HAuCl_4$ (10 mL, 1 mM) under vigorous stirring at ambient temperature for 6 h. The particle size of the formed AuNPs was 9 ± 1 nm. To estimate the concentration of gallic acid-capped AuNPs, we assumed that the reduction from gold(III) to gold atoms was 100% complete. According to this hypothesis, the concentration of gallic acid-capped AuNPs was calculated to be 40 nM. Metal ions (1–40 nM) were incubated with a solution containing gallic acid-capped AuNPs (0.63 nM), $NaClO_4$ (1 mM) and formic acid buffer (pH 4.5, 20 mM) for 20 min at ambient temperature. The scattering spectra were collected using the proposed detection system.

3. Result and discussion

3.1. Sensing of K^+ by salt-induced NP aggregation

Because the scattering cross section of a single AuNPs is proportional to the sixth power of its diameter [22], we initially investigated the effect of different-sized AuNPs (4, 15, 30, and 50 nm) on their light-scattering intensity in deionized water and $0.5\times$ PBS solution under irradiation with a 532-nm diode laser. The concentrations of different-sized AuNPs were all adjusted to 10^8 particles mL^{-1}. Note that the AuNPs are dispersed in deionized water, whereas they aggregated to large-sized particles in $0.5\times$ PBS. Salt-induced aggregation of the