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Review

Gold nanoparticle probes

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ABSTRACT

Depending on their size, shape, degree of aggregation and nature of the protecting organic shells on their surface, gold nanoparticles (AuNPs) can appear red, blue and other colors and emit bright resonance light scattering of various wavelengths. Because of this unique optical property, AuNPs have been extensively explored as probes for sensing/imaging a wide range of analytes/targets, such as heavy metallic cations, nucleic acids, proteins, cells, etc. Since their initial discovery, novel synthetic methods have led to precise control over particle size, shape and stability, thus allowing the modification of a wide variety of ligands on the AuNP surfaces to meet different experimental conditions. This review discusses the synthesis and applications of functionalized AuNPs in chemical sensing and imaging.

1. Introduction

The combination of nanotechnology with chemistry, biology, physics, and medicine for the development of ultrasensitive detection and imaging methods in the analytical or biological sciences is becoming increasingly important in modern science [1–14]. Particularly attractive is the use of functional AuNPs in biological and pharmaceutical field, such as the ultrasensitive detection and imaging methods for bioreorganizing events, because AuNPs have unique optical properties (i.e. surface plasma resonance absorption and resonance light scattering), a variety of surface coatings and great biocompatibility [5–7,11–18].

Generally, the optical properties of small metal nanoparticles are dominated by collective oscillation of electrons at surfaces (known as "surface plasmon resonance", SPR or "localized surface plasmon resonance", LSPR) that are in resonance with the incident electromagnetic radiation [4–6,13,19]. For gold, it happens that the resonance frequency of this oscillation, governed by its bulk dielectric constant, lies in the visible region of the electromagnetic spectrum [19]. Because nanoparticles have a high surface area to volume ratio, the plasmon frequency is exquisitely sensitive to the dielectric (refractive index) nature of its interface with the local medium. Any changes to the environment of these particles (surface modification, aggregation, medium refractive index, etc.) leads to colorimetric changes of the dispersions [5,8,20–25]. Due to coupling of the plasmons, assemblies (or aggregations) of AuNPs are often accompanied by distinct color changes. Colorimetric sensors using AuNPs have been widely explored and have important applications [6,8,14]. Not only is light strongly absorbed

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by the plasmons, it is also Rayleigh (elastically) scattered by them, and as the particle gets larger, a larger proportion of the outgoing light is scattered, compared with that absorbed [15,21]. Because the light scattered from AuNPs is in the visible portion of the electromagnetic spectrum in accord with their plasmon bands, it is possible to optically track the position of individual nanoparticles, paving the way for imaging applications [16,23,24]. The tailorable physical properties of AuNPs affect their collective oscillation of electrons offering tunable optical properties. This has further facilitated the application in biodetection via numerous detection methods [1–17]. The versatile surface chemistry of AuNPs could be achieved by linking various biofunctional groups, such as amphiphilic polymers, silanols, sugars, nucleic acids, and proteins, via the strong affinity of gold surface with thiol ligands [1–27]. Some of these studies have recently been reviewed elsewhere with a focus on the materials themselves or as subclassifications in more generalized overviews of biological applications of nanomaterials [1,3,5,6,8,12,14,15,20].

Here, without pretending to being exhaustive, we will focus on the preparation of spherical AuNP probes and AuNP based assays for ions, small molecules, DNA and protein detection and cellular analysis, highlighting some of their technical challenges and the new trends by means of a set of selected recent applications. We also note studies on non-spherical gold nanomaterials, gold nanorods (AuNRs) and gold nanoshells (AuNS, silica nanospheres with a nanoscale overcoat gold) which have tunable absorption in visible and NIR (700–1300 nm); these materials are the subject of other recent reviews [15,28,29].

2. Synthesis, stabilization and functionalization of gold nanoparticle probes

2.1. Synthesis

AuNPs are useful in a broad range of applications, but practical limitations are apparent when monodispersity is required. Numerous preparative methods for AuNPs from about 1 nm to several micrometers diameter are documented in the literature [30–41]. The most widely applied procedures to obtain ca. 10 to 150 nm gold hydrosols are variations of the classic Turkevich–Frens citrate reduction of gold (III) derivatives [30,31]. The AuNP size (between 10 and 147 nm) can be controlled by the ratio between the reducing/stabilizing agents (the trisodium citrate) and gold (III) derivatives (the hydrogen/sodium tetrachloroaurate (III)). This method is very often used even now since the rather loose shell of citrates on the particle-surfaces is easily replaced by other desired ligands (e.g., thiolated DNA) with valuable function [5,8].

Most hydrophobic AuNPs (also sometimes called monolayer-protected clusters (MPCs)) with diameters in 1 to ca. 8 nm ranges are prepared by the Brust–Schiffrin method: the gold (III) derivatives are reduced by sodium borohydride ($NaBH_4$) in an organic solvent in the presence of thiol capping ligands using either a two-phase liquid/liquid system or a suitable single-phase solvent [33,34]. In the Brust–Schiffrin methods, tetrachloroaurate (III) is transferred to toluene using tetraoctylammonium bromide (TOAB) as the phase-transfer reagent and reduced by $NaBH_4$ in the presence of dodecanethiol (DDT). Larger thiol/gold mole ratios give smaller average core sizes, and fast reductant addition and cooled solutions produced smaller, more monodisperse particles. Following the Brust–Schiffrin method, AuNPs with a variety of functional thiol ligands have been synthesized. Recently, a simple protocol for the one-step aqueous preparation of highly monodisperse AuNPs with diameters below 5 nm using thioether- or thiol-functionalized polymer ligands, such as alkyl thioether end-functionalized poly(methacrylic acid), has been developed by Hussain and co-workers [40–42]. In this approach, the particle size and size distribution is controlled by subtle variation of the polymer structure, concentration and "denticity". By varying systematically the polymer to gold ratio, the size of the nanoparticles can be finely tuned and a transition from non-fluorescent to fluorescent nanoparticles is observed for core diameters between 1.7 and 1.1 nm [42].

2.2. Stabilization and functionalization

For further AuNP applications, attaching the molecular recognition motifs (i.e. functional groups) of interest to the nanoparticles has to be readily achieved, and, most importantly, the probes must not bind non-specifically to each other or to anything else present in the system under investigation. In addition, introducing multiple functionalities would be of great value, as it provides more flexibility for multiplexing in bioanalytical applications and new tools to control the bottom-up assembly of nanostructures. Stabilization and functionalization of AuNP probes has been extensively reviewed elsewhere [1,5,6,8,10,14].

Electrostatic interaction, specific recognition (antibody–antigen, biotin–avidin, etc.), and covalent coupling (Au–S covalent, etc.) are three kinds of widely used methods to synthesis AuNP probes to meet the application requirement (as shown in Fig. 1) [1,3,5,6,8,12,14,15,20,43]. Electrostatic interaction or physical adsorption immobilization of ligands for AuNP probes is a simple process with the benefits of time saving and reduced complexity of ligand preparation [6,43,44]. Its relative simplicity gives this approach certain advantages over the more complex covalent immobilization methods. However, the binding is not strong enough to yield stable surfaces capable of standing the necessary washing steps and incubation conditions in biological studies on subsequent reaction. This issue is even more crucial in biological studies under harsh experimental conditions, for example, long time incubation with buffer solution which contains attacking molecules such as dithiothreitol (a small, uncharged molecule with two thiol groups, used to protect proteins from oxidation) as well as high salt concentration (generally used in DNA hybridization experiment). This results in a strong non-specific interaction between the AuNP probes and analytes which leads to decreased detection selectivity.

In comparison with the electrostatic interaction or physical adsorption immobilization techniques discussed above, covalent binding is normally more complex, sometimes requiring intensive synthesis work on the ligands. On the other hand, covalent binding of ligands with AuNPs offers high stability and is demonstrated to be quite robust: they can withstand a very high salt concentration (e.g., 2 M NaCl); they are extremely stable under thermal

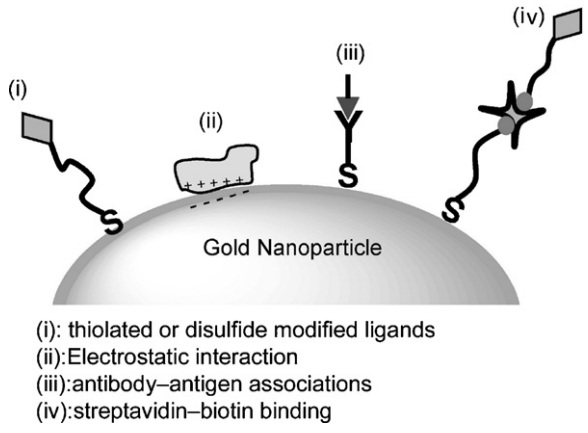

Fig. 1. Schematic representation of formation of gold nanoparticle probes.