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A survey of place-exchange reaction for the preparation of water-soluble gold nanoparticles

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ABSTRACT

Water-soluble gold nanoparticles (AuNPs) have gained considerable attention because they offer a myriad of potential applications, especially in the fields of biology and medicine. One method to prepare such gold nanoparticles is through the well-known Murray place-exchange reaction. In this method, precursor gold nanoparticles, bearing labile ligands and with very good size distribution, are synthesized first, and then reacted with a large excess of the desired ligand. We report a comparison of the reactivity of several known precursor gold nanoparticles (citrate-stabilized, pentanethiol-stabilized, tetraoctylammonium bromide-stabilized, and 4-dimethylaminopyridine-stabilized) to several biologically relevant ligands, including amino acids, peptides, and carbohydrates. We found that citrate-stabilized and 4-dimethylaminopyridine-stabilized gold nanoparticles have broader reactivities than the other precursors studied. Citrate-stabilized gold nanoparticles are more versatile precursors because they can be prepared in a wide range of sizes and are very stable. The hydrophobic pentane-stabilized gold nanoparticles made them "inert" toward highly water-soluble ligands. Tetraoctylammonium bromide-stabilized gold nanoparticles exhibited selective reactivity, especially for small, unhindered and amphiphilic ligands. Depending on the desired ligand and size of AuNPs, a judicious selection of the available precursors can be made for use in place-exchange reactions. In preparing water-soluble AuNPs with biologically relevant ligands, the nature of the incoming ligand and the size of the AuNP should be taken into account in order to choose the most suitable place-exchange procedure.

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1. Introduction

Water-soluble gold nanoparticles (AuNPs) have been of great interest for a number of years for their wide range of potential applications, such as sensing [1], catalysis [2], drug delivery [3–5], and imaging [6,7]. After the discovery of the synthesis of size-controllable citrate-stabilized AuNPs by Turkevich [8] and Frens [9], there has been a constant effort to improve and complement the preparation of AuNPs. For example, Brust and co-workers [10,11] have paved the way in synthesizing stable, size-controllable (1.5–5.2 nm size), and functionalizable AuNPs. In one of these reactions [11], AuNPs were synthesized by mixing an organothiol and a gold salt ($AuCl_4^-$) in the same solvent under reducing conditions. Another method involves the formation of precursor AuNPs bearing weakly bound ligands, followed by the reaction with an excess of the desired organothiol to form the AuNPs [10]. The latter method, which is also known as the Murray place-exchange reaction [12], is very attractive because it offers both more control over particle size and more flexibility in the nature of the coating ligands employed. Murray and co-workers have extensively studied place exchange reactions, especially those involving the formation of alkylthiolate-stabilized AuNPs [12–15]. The precursor AuNPs for place-exchange reactions can vary in size and/or passivating ligand. Several known AuNPs, such as the citrate-stabilized [8,9], alkanethiolate-stabilized [10], dimethylaminopyridine (DMAP)-stabilized [16,17], and tetraoctylammonium bromide (TOAB)-stabilized AuNPs [10], are potential precursors or starting materials for ligand-exchange reactions. Although numerous studies have examined this process in detail [12–15], the mechanism is still not fully understood. Nevertheless, this reaction provides access to water-soluble AuNPs with very uniform size distributions and ligand control.

In the advent of a multitude of applications of water-soluble AuNPs, the need for robust ligand-exchange methods has never been more crucial. A better understanding of the reaction may prove useful in choosing the appropriate method of AuNP preparation. In this study, we evaluated four precursors (citrate-stabilized, pentanethiolate-stabilized, TOAB-stabilized, DMAP-stabilized AuNPs) for place-exchange reaction using a wide variety of biologically relevant water-soluble ligands (Fig. 1). Representative ligands

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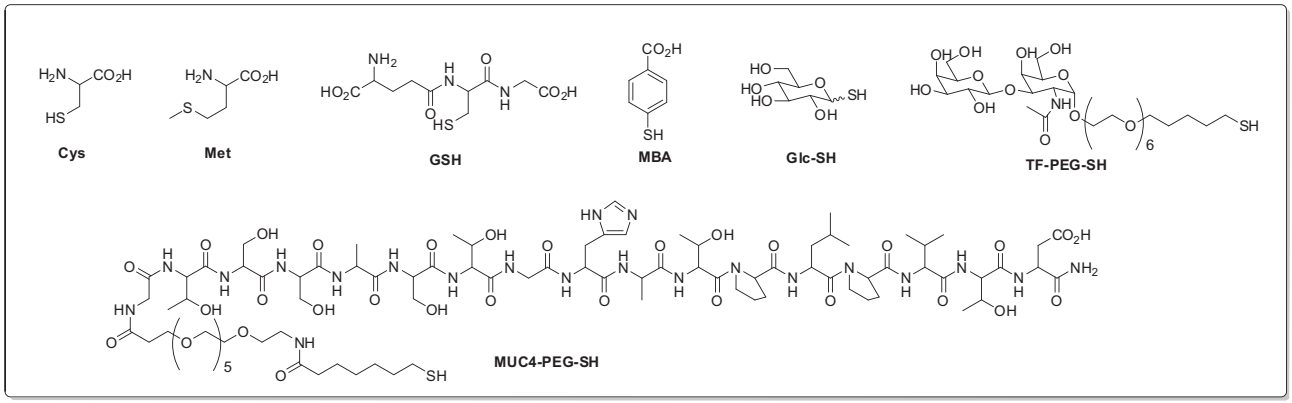

Fig. 1. Model water-soluble ligands used for place-exchange reactions.

included the amino acids cysteine (**Cys**) and methionine (**Met**), the tripeptide biological antioxidant, glutathione (**GSH**), 4-mercaptobenzoic acid (**MBA**), thioglucose (**Glc-SH**), the Thomsen–Friedenreich tumor antigen disaccharide attached to a polyethylene glycol (PEG) linker [18] (**TF-PEG-SH**) and 16-mer peptide derived from the tandem repeat sequence of the membrane associated mucin MUC4 [19] attached to a similar PEG linker (**MUC4-PEG-SH**) [20]. These compounds were chosen to represent different sizes, classes, and polarity of water-soluble ligands that are of biological importance. We were able to classify the degree of reactivity of the precursors based on the number of ligands that bound to the AuNP. In addition, we were also able to deduce some structural and physical requirements of the ligands for a particular precursor (i.e. size, polarity, amphiphilicity, charge).

2. Experimental

2.1. General remarks

$HAuCl_4{\cdot}XH_2O$ was purchased from Strem Chemicals and used as received. Sodium borohydride, pentanethiol, tetraoctylammonium bromide, cysteine, methionine, thioglucose sodium salt, 4-mercaptobenzoic acid, and dimethylaminopyridine were purchased from Sigma–Aldrich Corp. and were used as received. Compounds **TF-PEG-SH** and **MUC4-PEG-SH** were synthesized following the literature procedure [18,20]. Water was obtained from a Millipore Milli-Q plus purification system (resistivity of 18.2 MΩ/cm). UV–visible spectra were recorded on an Agilent 8453 spectrophotometer. Citrate-stabilized AuNPs (5 nm) were purchased from Ted Pella, Inc., and used as received. ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrometer at 25 °C. TEM samples were prepared by placing an aqueous solution (~2 μl) of the AuNPs on the grid with a carbon-coated support film that was previously treated with glow discharge. The excess liquid was blotted with a filter paper, allowed to dry, and rinsed with distilled water twice. TEM images were taken using a Hitachi H7650 TEM (Tokyo, Japan) operating at 80 kV with a 2 k × 2 k CCD camera (AMT; Danvers, MA). The sizes of Au NPs were analyzed using the camera's measurement software (AMT).

2.2. Synthesis of pentanethiol-stabilized Au NPs

Pentanethiol-stabilized AuNPs were prepared following a literature procedure [21] adapted from the original Brust protocol [10]. Briefly, a solution of aqueous $HAuCl_4$ (30 mM, 30 mL) was mixed with a toluene solution of tetraoctylammonium bromide (50 mM, 80 mL). Pentanethiol (170 mg, 0.84 mmol) was then added, followed by the slow addition of $NaBH_4$ solution (0.4 M, 25 mL). The mixture was stirred for 10 min at room temperature, the organic layer was collected and concentrated by rotary evaporation to ~10 mL. Ethanol (500 mL) was added, and the mixture was kept at 4 °C overnight. The precipitate was collected by centrifugation, redissolved in toluene, and re-precipitated by the addition of ethanol. After cooling the mixture at 4 °C, the dark brown precipitate was collected and dried under vacuum overnight.

2.3. Synthesis of 4-(dimethylamino)pyridine-stabilized Au NPs

DMAP-stabilized Au NPs were prepared a following literature procedure [22]. A toluene solution of TOAB (612 mg in 20 mL) was mixed with an aqueous solution of $HAuCl_4$ (100 mg in 8 mL). The heterogeneous mixture was vigorously stirred until all of the gold salt had transferred to the organic phase. A freshly prepared sodium borohydride solution (105 g in 6 mL) was added slowly and the mixture was stirred for 12 h at room temperature. The organic layer was collected; washed with water 3×; and dried with anhydrous Na_2SO_4. The volume of solution was adjusted to 50 mL by addition of toluene. A solution of 4-(dimethylamino)pyridine in water (610 g, 50 mL) was added and the mixture was stirred until phase transfer was complete (i.e., all of the color transferred to the aqueous phase). The dark red mixture was isolated and stored at 4 °C.

2.4. Synthesis of tetraoctylammonium bromide-stabilized Au NPs

The preparation of tetraoctylammonium bromide-stabilized Au NPs was done according to the method used of Brust et al. [10] as described above in the preparation of pentanethiol-stabilized Au NPs.

2.5. General procedure for the reaction of precursor nanoparticles with various ligands

2.5.1. Using citrate-stabilized Au NPs

Commercially-available citrate-stabilized gold nanoparticles (5 nm, ~1 nM) was mixed with a 200-fold excess of the ligands (relative to the concentration of the AuNPs), and the resulting mixture was stirred for 1–72 h. The progress of reaction was monitored by UV–vis spectroscopy.

2.5.2. Using pentanethiol-stabilized Au NPs

The pentanethiol-stabilized Au NPs (1 mL of 10 mg/mL solution in toluene) were reacted with the model ligands in water for 1 h at 25 °C. The reaction was monitored by visually inspecting for the phase transfer of the AuNPs.