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Multidentate-Protected Colloidal Gold Nanocrystals: pH Control of Cooperative Precipitation and Surface Layer Shedding

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Abstract

Colloidal gold nanocrystals with broad size tunability and unusual pH-sensitive properties have been synthesized by using multidentate polymer ligands. Containing both carboxylic functional groups and sterically hindered aliphatic chains, the multidentate ligands are able to both reduce gold precursors and to stabilize gold nanoclusters during nucleation and growth. The “as-synthesized” nanocrystals are protected by an inner coordinating layer and an outer polymer layer, and are soluble in water and polar solvents. When the solution pH is lowered by just 0.6 units (from pH 4.85 to 4.25), the particles undergo a dramatic cooperative transition from being soluble to insoluble, allowing rapid isolation, purification, and redispersion of the multidentate-protected nanocrystals. A surprise finding is that when a portion of the surface carboxylate groups is neutralized by protonation, the particles irreversibly shed their outer polymer layer and become soluble in nonpolar organic solvents. Further, the multidentate polymer coatings are permeable to small organic molecules, in contrast to tightly packed self-assembled monolayers of alkanethiols on gold. These insights are important towards the design of “smart” imaging and therapeutic nanoparticles that are activated by small pH changes in the tumor interstitial space or endocytic organelles.

Colloidal gold nanocrystals are a class of “plasmonic” nanostructures with size-dependent electronic, optical, and chemical properties¹. They are currently under intense research and development for applications in bionanotechnology,² surface-enhanced Raman scattering (SERS),³ photothermal therapy,⁴ as well as for in-vivo delivery of therapeutic and imaging agents.⁵ Unlike semiconductor quantum dots (QDs) that often contain cadmium or other toxic elements,⁶ colloidal gold has been used to treat rheumatoid arthritis in humans for over 20 years, and is believed to be largely nontoxic and safe.⁷ At the present, two major approaches are widely used for chemical synthesis of high-quality gold nanoparticles. The first approach is based on the method of Turkevich and Frens, in which sodium citrate is used as a reducing agent and a stabilizing ligand.⁸ While the particle size can be controlled by the molar ratio of gold precursors to citrate, the resulting nanocrystals are not well protected and are prone to aggregation upon storage or when exposed to salts. The second approach is based on the method of Brust and Schiffrin, in which alkanethiols are used to stabilize gold particles in a two-phase emulsion process.⁹ This method yields monolayer-protected gold clusters that are highly stable, but the available range of nanoparticle sizes is limited to only 1 - 5 nm.^{9,10}

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Supporting Information Available: Detailed procedures for chemical synthesis of gold nanocrystals, preparation of spectrally encoded SERS nanoparticles, schematic diagram of the multidentate polymer ligands, and additional nanoparticle size and charge data (Supporting Figures S1 to S5). This material is available free of charge via the Internet at <http://pubs.acs.org>.

Here we report a new strategy based on the use of multidentate polymer ligands to synthesize protected gold nanocrystals with broad size tunability and pH-sensitive surface properties. The carboxylic acid functional groups of the polymer ligands are able to coordinate with the surface atoms of the nanocrystals and behave in the same manner as common capping ligands.⁸ However, the large number of functional groups from the polymer considerably alters the nucleation and growth kinetics of nanocrystals in comparison to the monovalent ligands used previously.⁸⁻¹⁰ Each polymer molecule has approximately 14 carboxylic groups available for binding to the nanocrystal surface (see Supporting Information). This multidentate effect significantly increases the binding affinity of the ligand and results in an extremely stable surface coating. The surface coating also contains a large number of extended alkyl chains that are able to interact with the hydrophobic side chains of the free polymer, leading to a thick hydrophobic middle layer and a hydrophilic outer layer (exposed carboxylic acid groups). As a result, highly stable gold nanocrystals have been prepared with tunable sizes from 5 nm to 150 nm. As discussed in more detail below, the multidentate-protected nanocrystals can be isolated, purified, and redispersed, practically behaving as chemical reagents.

As shown in Figure 1a, immediately after synthesis, the gold nanocrystals are protected by an inner coordinating layer and an outer polymer layer, and are soluble in water and polar solvents. Transmission electron microscopy reveals a thick polymer coating around the gold nanocrystals (Figure 1c and Supporting Figure S2). When a portion of the surface carboxylate groups is neutralized at a lower pH, the nanocrystals irreversibly shed their outer polymer layer and become soluble in nonpolar organic solvents such as chloroform. After the loss of this outer polymer layer, the nanocrystals are encapsulated by a single layer of the multidentate ligands, and their hydrodynamic size decreases by 15-20 nm (Figure 1b). This large size decrease indicates that the inner coordinating layer (formed by multidentate binding) is much tighter than the outer polymer layer (consisting of a hydrophobic layer and exposed carboxylic acid groups). We find that there are two conditions for this outer layer shedding to occur: (i) the surface charges need to be neutralized at acidic pHs (below the pK_a value of acetic acid); and (ii) the charge-neutralized nanocrystals need to be exposed to a nonpolar solvent such as chloroform. Once the outer layer is lost, the nanocrystals are only soluble in nonpolar solvents and cannot be redissolved in water or polar solvents (unless excess polymer ligands are added). This irreversible behavior rules out the possibility of a single loose polymer layer, which would be expected to reversibly expand and contract in response to pH.

As shown in Figure 2, the use of multidentate polymer ligands gives rise to novel nucleation and growth mechanisms in comparison with monovalent ligands. With the traditional citrate method, the nucleation and growth of gold nanocrystals undergo a transient stage in which the solution initially becomes clear (reduction to atomic Au clusters) and subsequently progresses to a grey intermediate before developing the characteristic ruby-red color of gold colloids (Figure 2a). This is confirmed by monitoring the absorbance, which first shows a broad absorption spectrum (*black curve*) that rapidly blue-shifts and narrows to form the surface plasmon resonance peak typical of monodisperse gold nanocrystals (*red curve*). The transient intermediate is noticeably absent when preparing nanocrystals using the multidentate polymer ligand (Figure 2b), indicating the polymer-induced nanocrystal formation proceeds through different nucleation and growth mechanisms.¹¹ Using this method, gold nanocrystals slowly appear and increase in concentration as the synthesis progresses. Absorption spectra measured during nanocrystal growth illustrate the appearance and gradual red-shifting of the surface plasmon resonance peak (see Figure 2b).

An important finding is that the nanocrystals growth rate is reduced by nearly two orders of magnitude in comparison with that reported for monovalent ligands.⁸⁻¹⁰ The increased

binding affinity of the multidentate ligand certainly reduces the rate at which elemental Au atoms are added to the growing particles, but this effect cannot completely account for the large difference in kinetic rates. Further experimental studies using similar polymers *without hydrophobic alkyl chains* have shown that the growth kinetics is reduced by only one order of magnitude. Thus, the additional growth retardation is due to steric hindrance effects of the multidentate polymer coating, as has been observed in the synthesis of other nanocrystals.¹² This is an important insight because slower growth kinetics allows a better control of the nanocrystal size. The gold nanocrystal size can also be tuned by changing the ratio of polymer ligands to Au atoms, in the same manner as particles synthesized by citrate reduction.⁸ By using these two strategies, we have succeeded in preparing multidentate-protected gold nanocrystals across a large size range between 5 nm to 150 nm (with ~10% size variations) (Supporting Figures S3 and S4).

The multidentate-protected gold nanocrystals are immediately soluble in water and polar solvents such as dimethylformamide and acetone (Figure 3a). However, adding water-soluble gold nanocrystals to nonpolar solvents such as chloroform results in two separate phases, with the negatively charged nanocrystals remaining in the aqueous phase (Figure 3b). As discussed earlier, when the surface charge is reduced at lower pH's, the nanoparticles rapidly shed their outer polymer layer, exposing hydrophobic alkyl chains. This process can be used to transfer gold nanocrystals of a wide size range into a variety of nonpolar solvents. Furthermore, in contrast to citrate stabilized particles that aggregate at 10 mM or higher salt concentrations, the polymer coated gold nanocrystals are highly resistant to salt induced aggregation at concentrations as high as 2.5 M (shown by the surface plasmon resonance peak in Figure 3c). The particles also exhibit high stability in serum solutions, suggesting that the polymer coated gold nanocrystals are likely well suited for biodiagnostic applications under complex conditions.

As shown in Figure 4a, the protected nanocrystals are sensitive to pH, and can be precipitated and isolated under acidic conditions. The precipitated nanocrystals can be subsequently purified and redissolved by raising the solution pH to 6 or 7. Significantly, nanoparticle precipitation takes places in a pH range that is much narrower than the titration curve of carboxylic acid (see Figure 4b). Based on the fitted experimental data, we estimate that 95% of the particles are soluble at pH=4.85, while only 5% of the particles are soluble at pH=4.25. This sharp transition from solubility is triggered by a pH change of only 0.6 units. Assuming that the acid-base equilibrium follows closely with the titration curve, this solubility transition corresponds to a 40% change in carboxyl neutralization (from 35% neutral carboxyl groups (-COOH) at pH 4.85 to 75% neutral groups at pH 4.25).

It is worth noting that Mirkin and coworkers¹³ have reported a strongly cooperative effect for DNA-conjugated gold nanoparticles, leading to very sharp “melting” curves and improved specificity for discrimination of single-base mismatches. The observed cooperativity is believed to arise from a dependence of the oligo melting temperature on the local salt concentration (localized counterions that are needed to neutralize the charges on oligonucleotides).^{13a} Here we believe that cooperative precipitation arises from a “magnifying” process in which extensive nanoparticle aggregation is triggered by small changes in surface charge and hydrophobicity (see Figure 4c). Both electrostatic and hydrophilic/hydrophobic interactions are likely to be important. At pH values above the pKa of carboxylic acids, most of the functional groups are deprotonated, and the charged nanoparticles are stabilized by electrostatic repulsion (Supporting Figure S5). As the pH approaches the pKa, a portion of these carboxylic acid groups become protonated and thus lose their charges and becomes more hydrophobic. A threshold is then reached where the diminishing electrostatic repulsion is no longer able to counteract the van der Waals and hydrophobic interactions, leading to a precipitation cascade and the sharp transition seen in

the stability curve. Recent work by Gao and coworkers¹⁴ has shown a similar cooperative effect in which small pH changes are able to disrupt the thermodynamic stability of self-assembled polymer nanoparticles, triggering the release of encapsulated imaging or therapeutic agents. Designed for targeting specific endocytic organelles in living cells, their nanoparticles probes show a signal response (fluorescence intensity change) as much as 50-fold when the pH is changed by only 0.25 units.

Finally, the multidentate polymer coatings are found to be permeable to small molecules such as organic dyes. This is surprising because electron microscopy has shown that the polymer coatings are fairly thick, with little to no defects (Figure 1c). Unlike small monovalent ligands such as alkanethiols which are able to pack closely on gold surfaces,¹⁵ it is possible that the random adsorption of multidentate polymers to the growing nanocrystal could leave “empty” patches on the particle surface. These regions are protected by the overall corona of the surrounding polymers but are available to bind small molecules that can diffuse through the polymer coating. The experimental evidence comes from surface-enhanced Raman scattering (SERS) studies in which the reporter molecules must move across the polymer coating and then adsorb on the gold nanocrystal.³ Previous work has shown that gold nanocrystals with a diameter of 60-70 nm are optimal for surface Raman enhancement (at 633-647 nm excitation).¹⁶ We have thus optimized the polymer concentration and reaction time of the synthesis procedure to prepare gold nanocrystals with an average diameter of 60 nm. After the addition of a Raman reporter dye (malachite green), the gold nanocrystals exhibit strong SERS signals (Figure 5), closely matching the reference spectrum obtained from SERS particles prepared using previously reported methods.^{16b} Several new peaks are observed from the multidentate-coated particles, likely due to surface enhancement of the strongly adsorbed carboxylate groups and the polymer backbone. However, these peaks are absent in the control spectrum, and further studies are needed to determine the molecular origins of these peaks.

In summary, we have developed a new strategy based on multidentate polymer ligands to synthesize colloidal gold nanocrystals with broad size tunability and pH-sensitive properties. The “as-synthesized” nanocrystals are protected by an inner coordinating layer and an outer polymer layer, and are broadly soluble in water and polar solvents. The protected particles are shown to undergo a pH-dependent transition in solubility, allowing rapid isolation, purification, and redispersion of the multidentate-protected nanocrystals. When a portion of the surface carboxylate groups is neutralized at a lower pH, the particles can further shed their outer polymer layer and become soluble in nonpolar organic solvents in an irreversible manner. In contrast to tightly packed monolayers of alkanethiols on gold, the multidentate polymer coatings are permeable to small organic molecules, allowing the preparation of spectrally-encoded SERS nanoparticles for medical diagnostic and imaging applications. Such stable and permeable surface coatings are also expected to be important in nanoparticle-based catalysis for which the reactants need to diffuse through the polymer layer, and the products to diffuse out.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(a) Schematic illustration of multidentate-protected gold nanocrystals with pH-sensitive properties including solubility control by surface charge (**1 and 2**) and outer layer shedding (**2 and 3**) (not to scale). (b) Dynamic light scattering data showing a dramatic change in the hydrodynamic size of gold nanocrystals after surface layer shedding. (c) Transmission electron micrographs showing a thick polymer coating (white) surrounding water-soluble gold nanocrystals (top). After outer layer shedding, particles in chloroform show a much thinner polymer shell (bottom). Note that the chain-shaped arrangement of nanoparticles was an artifact caused by drying on the TEM grid.

Figure 2.

Comparison of gold nanocrystal nucleation and growth kinetics as observed with traditional monovalent or multidentate polymer ligands. (a) Color photograph (*top*) and absorption spectra (*bottom*) at different reaction times during the citrate reduction procedure. (b) Color photograph (*top*) and absorption spectra (*bottom*) at different reaction times during nanoparticle synthesis in the presence of multidentate ligands. The numbers (2 and 8) in the absorbance spectra correspond to the numbers of the vials. The reaction time for completion was ~9 hours for the multidentate procedure, more than 50-fold longer than that (10 minutes) of the citrate procedure.

Figure 3.

Broad solubility and stability of multidentate polymer-coated gold nanocrystals. (a) Color photograph showing stable gold nanocrystals dissolved in a broad range of solvents. (b) Color photograph showing extraction of nanocrystals into the water phase at basic pH, and extraction into the organic phase (chloroform) at acidic pH. (c) Absorption spectra in the presence of 0.1 M to 2.5 M NaCl.

Figure 4.

pH-triggered cooperative transition in solubility as measured by precipitation of multidentate-protected gold nanocrystals. (a) Plots of gold nanocrystal solubility (*black curve*) and the degree of carboxylic acid deprotonation (*red curve*) as a function of pH. The solubility curve closely mirrors the titration curve of acetic acid, but is much sharper due to a cooperative effect (see text). (b) Hydrodynamic light scattering data as a function of pH, showing the formation of nanoparticle aggregates at lower pHs. (c) Schematic illustration of pH-triggered precipitation of nanoparticles. Surface carboxylate ions are protonated as pH decreases, resulting in a decrease in electrostatic repulsion and eventual precipitation from solution.

Figure 5.

Surface-enhanced Raman scattering (SERS) studies demonstrating that small reporter molecules are able to move across the multidentate polymer coating and to adsorb on the gold surface. The SERS spectra were obtained from 60-nm multidentate-protected gold nanocrystals. *Red curve*: negative control (multidentate-coated gold nanoparticles without the reporter dye); *black curve*: SERS spectra of multidentate-protected gold nanocrystals after the addition of malachite green isothiocyanate or MGITC; and *green curve*: standard SERS nanoparticles encoded with MGITC. Excitation wavelength = 633 nm; laser power = 3 mW; integration time = 1 second.