

Gold Nanocages: Recent Developments in Synthesis and Payload Delivery

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Nanomaterials have been increasingly studied as catalysts, bioimaging agents, and drug delivery systems. Gold nanoparticles in particular are exceptionally useful nanomaterials due to the sensitive optical and catalytic properties caused by a localized surface plasmon resonance (LSPR) effect that occurs upon irradiation.¹ Gold nanocages (AuNCs) are a specific class of gold nanoparticles composed of porous gold shells and hollow centers. Nanocages are distinguished from standard gold nanoparticles, which are nonporous particles with dense. The unique properties of AuNCs make them excellent candidates for nanocatalytic centers and drug delivery vehicles.²

AuNCs have increased surface area compared to traditional gold nanoparticles, and their unique hollow interiors allow for small molecules to be stowed inside and then released.² Using gold nanocages for biological applications is advantageous due to the tunability of AuNCs for near-IR activity and their non-toxic properties for many cell types.³ Nanoparticles that absorb light in the near-IR region (700-2500 nm wavelengths of light) take advantage of the “transparent window” of live tissue, which can easily be penetrated by near-IR light.⁴ However, one drawback of using NIR-responsive nanocages in living tissues is that functional depth is limited to several centimeters.⁵ To address this issue, nanocages can also be used without external stimulus, relying on surface functionalization and diffusion into and out of gold nanocages. Using gold nanocages is desirable because their hollow interiors and increased surface area allow more molecules to be attached to the particle per volume.¹ Increased surface functionality can lead to increased catalytic function, increased payload delivery to target tissues, and intensified optical properties.

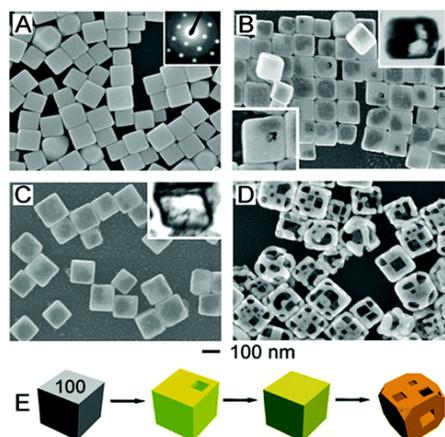
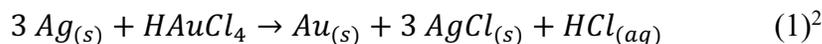


Figure 1. Example of early preparation of AuNCs. SEM of Ag nanocubes with various amounts of 1 mM HAuCl₄. (A) 0 ml, (B) 0.3 ml, (C) 0.5 ml, (D) 2.25 ml. (E) Schematic of changes in AuNCs.²

The earliest attempts to synthesize AuNCs involved galvanic replacement of gold onto a sacrificial template, combining the formation of the Au shell and removal of the template in a single experimental step.¹⁻⁸ The Xia group first synthesized gold nanocages over silver nanocubes using a titration-like method.² During a typical preparation, initiation occurs at the site of a point defect in the silver template, then gold is reduced from HAuCl₄ to atomic Au on the surface of the Ag nanocube. As the amount of HAuCl₄ is increased, Ag is selectively dealloyed and stabilized in solution at reflux temperatures by available Cl⁻ (Eq. 1); as dealloying progresses, surface holes and eventually the Au shell are created from a loss of Ag from the Ag-Au alloy (Figure 1).² The mechanism of initiation, galvanic replacement, and dealloying is largely deduced from TEM images of AuNCs prepared by adding varying amounts of HAuCl₄.



Additional synthetic strategies for the preparation of gold nanocages have since been developed to improve tunability and size, and provide different morphology. In 2017, Xia and coworkers synthesized icosahedral AuNCs using a chemical etchant to dissolve the palladium template nanoparticle (Figure 2).⁶ Chemical etching leaves random pores in the approximately 3-5 nm gold coating, converting core-shell nanoparticles to AuNCs.⁶ Similar to earlier syntheses, the

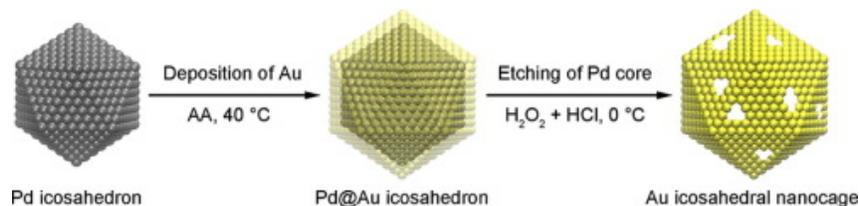


Figure 2. Synthesis of 12 nm icosahedral nanocages by making a palladium sacrificial scaffold and etching away the core.^b

amount of etchant added determines the LSPR of the nanoparticle, but Pd-based AuNCs are much smaller, at about 12 nm compared to the tunable 30-200 nm seen for AuNCs made from Ag nanoparticles.^{2,6} Pd-based AuNCs, unlike Ag-based AuNCs, can form at low temperatures (0°C and 20°C) because of the solubility of palladium chloride in cold aqueous solution, offering the previously unachieved advantage of tuning the porosity by controlling the number of vacancies.⁶

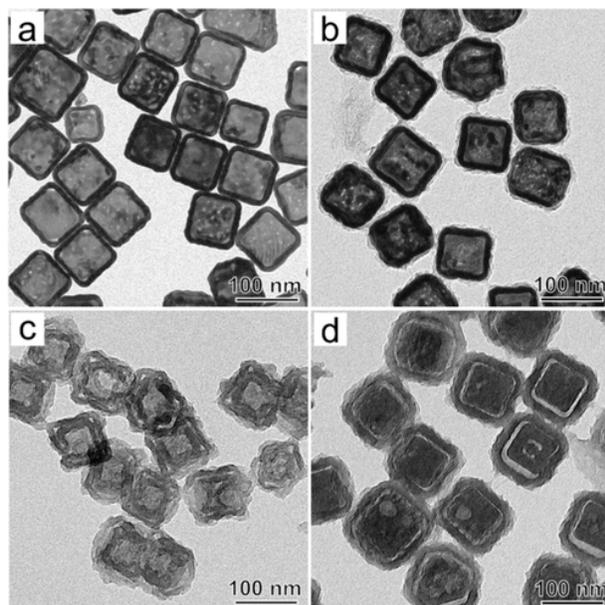
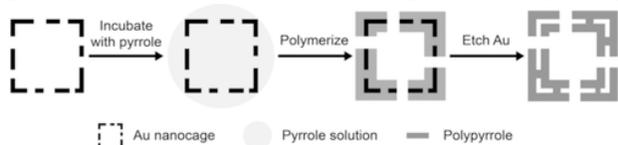


Figure 3. (Top) Overview of polymerization of pyrrole on inner and outer surfaces of AuNCs. (Bottom) TEM images of (a) 80 nm AuNCs, (b) PPy-coated AuNCs, (c,d) double-walled PPy shells after Au etching.⁷

The primary advantage of using AuNCs is the increased surface area for functionalizing molecules. However, it is difficult to quantify the amount of compound successfully attached to the particle. One study sought to demonstrate that the amount of a particular molecule on the outer and inner surfaces could be tracked using a polymer that coats the entire surface area. By using iron (III) chloride to catalyze the polymerization of pyrrole, etching away the porous gold shells, and measuring wall thickness of the remaining polymer, Yang and coworkers were able to observe the effect of polymerization on inner and outer surfaces.⁷ There was a correlation between the thickness of the walls of the poly(pyrrole) (PPy) and the concentration of pyrrole added to the solution with AuNCs. When incubated with 4.6 mM pyrrole for 3 hours, AuNCs had a 9 nm coating on both the inner and outer surfaces; when the concentration was increased to 9.3 mM, the outer polymer shell thickness increased to 15 nm, while the inner polymer shell completely filled the cage (approximately 32 nm) (Figure 3).⁷ This result was attributed to the local increase in concentration of pyrrole induced by AuNCs.⁷ The TEM images provide insight into

the effects of AuNCs on polymerization as well as compound-loading, but does not allow for direct measurement (e.g. molecular weight or degree of polymerization). The Xia group compared the deposition of species onto the inner and outer surfaces of AuNCs with palladium rather than organic compounds.⁹ This study, which more accurately tracked the amount of Pd used to coat the inner and outer surfaces, but determined that the kinetics of the reduction dominates the reaction.⁹ These two investigations primarily considered coating thickness to model AuNC loading mechanisms rather than quantitatively analyzing the number of species.

Practical studies of molecule loading into and catalytic activities of AuNCs are not as straightforward as previously discussed models. In 2021, Hu and coworkers loaded spherical AuNCs with IR-780, a fluorescent dye, using F-127, a hydrophilic surfactant.¹⁰ The loading efficiency (percent of dye available that is loaded into AuNCs) was 21.7% and the loading content (percent of available sites covered with dye) was 5.7%. Most nanocarriers have a loading content under 10%, and although this loading mechanism is an improvement over that possible with solid gold nanoparticles, it is not exceptional.¹⁰ A comparable study loaded an anti-cancer agent into cubic AuNCs and achieved three times the loading content.¹¹ In another study, the effect of increased surface area provided by AuNCs was demonstrated in the reduction of gaseous nitrogen to ammonia.¹² The El-Sayed group used AuNCs to achieve then-unprecedented Faradaic efficiency of 30.2% for the electrochemical reduction of ammonia, compared to the 10-20% achieved by standard industrial procedures. They theorized that AuNCs yield higher efficiency due to increased surface area and number of atoms with unsatisfied valency.¹²

Although the hollow centers of AuNCs enable increased payload capacity, the porous shell is a simultaneous advantage and disadvantage. The porosity allows small molecules to freely diffuse in and out of the gold layer. Polymeric and metallic coatings can provide insight to the properties of AuNCs provided by increased surface area and ability for local entrapment. However, practical applications must be further investigated to determine the advantages of using AuNCs over other catalysts and nanoparticles.

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