Gold Nanotetrapods with Unique Topological Structure and **Ultranarrow Plasmonic Band as Multifunctional Therapeutic Agents**

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Supporting Information

ABSTRACT: Owing to their excellent surface plasmonic properties, Au nanobranches have drawn increasing attention in various bioapplications, such as contrast agents for photoacoustic imaging, nanomedicines for photothermal therapy, and carriers for drug delivery. The monodispersity and plasmonic bandwidth of Au nanobranches are of great importance for the efficacy of those bioapplications. However, it is still a challenge to accurately synthesize size- and shape-controlled Au nanobranches. Here we report a facile seed-mediated growth method to synthesize monodisperse Au nanotetrapods (NTPs) with tunable and ultranarrow plasmonic bands. The NTPs have a novel D_{2d} symmetry with four arms elongated in four $\langle 110 \rangle$ directions. The growth mechanism of NTPs relies on the delicate kinetic control of deposition and diffusion rates of adatoms. Upon laser irradiation, the PEGylated NTPs possess remarkable photothermal conversion efficiencies and photoacoustic imaging



properties. The NTPs can be applied as a multifunctional theranostic agent for both photoacoustic imaging and image-guided photothermal therapy.

u nanoparticles have been a subject of intense research for A a wide range of biological and biomedical applications.¹⁻⁴ Among Au nanoparticles, Au nanobranches with noticeable arms have drawn enormous interest for bioapplications owing to their excellent localized surface plasmon resonance (LSPR) properties in the NIR region.⁵ For instance, both their sharp branches and high surface-to-volume ratios play important roles in enhancing the conversion of light to heat energy.^{6–8} In addition, Au nanobranches show higher cellular uptake,⁹ lower cytotoxicity, significant long blood circulation, and high tumor accumulation in pharmacokinetic studies.¹⁰ These advantages make Au nanobranches attractive for multiple bioapplications such as theranostic agents for bioimaging¹¹⁻¹³ and photothermal cancer treatment^{14,15} and drug carriers.^{16,17} However, the majority of these applications use a single-wavelength laser for excitation of the Au nanobranches with corresponding LSPR peak.^{18–20} As a result, a narrow LSPR band is beneficial to improve the efficacy of those applications, indicating that size and structurally homogeneous Au nanobranches are highly desired. However, the controlled synthesis of Au nanobranches has been extremely difficult because of symmetry breaking growth of the face-center-cubic nanocrystals.²¹ Naturally, it is more challenging to synthesize Au nanobranches with accurate control in terms of the number, size, spatial arrangement of branches, high yield, and repeatability.²²⁻²⁵

Received: June 3, 2019 Accepted: July 16, 2019 Published: July 16, 2019 Herein, we demonstrate the synthesis of monodisperse single-crystalline nanotetrapods (NTPs) in high yield via a facile seed-mediated method. NTPs with narrow size distributions exhibit an extremely narrow LSPR peak with a full width at half-maximum (fwhm) of only 91 nm (0.20 eV), which is much smaller than those of Au nanobranches reported in the literature. The NTPs have a unique, unusual D_{2d} symmetry, with tunable arm lengths, well-defined structure, and surface facets. The growth of four arms along $\langle 110 \rangle$ directions is a kinetically controlled process. In addition, NTPs show outstanding photothermal conversion efficiencies and photoacoustic imaging properties when exposed to an 808 nm laser.

Monodisperse NTPs in high yield were synthesized through a seed-mediated approach. The single-crystalline 1–2 nm Au seeds were synthesized using a previously reported approach for the preparation of Au nanorods.²⁶ After addition of aged Au seeds to a growth solution which comprised HAuCl₄, ascorbic acid (AA), and hexamethylenetetramine (HMT) in the presence of hexadecyltrimethylammonium bromide (CTAB) as a surface capping agent, the color of the solution changed from colorless to deep bluish in ca. 5 min, suggesting the complete formation of NTPs. HMT mainly acted as a reducing agent for HAuCl₄ (vide infra).²⁷ The transmission electron microscopy (TEM) image (Figure 1a) of the NTPs



Figure 1. (a) TEM image of NTPs. (b) UV-vis-NIR spectrum of NTPs in solution. (c) Dark-field scattering spectrum and correlated SEM image of a single NTP. Scale bar: 20 nm.

shows a remarkable high yield: 85% of NTPs obtained under the optimized synthetic condition. TEM analysis reveals that the NTPs are uniform with an average arm length of 20.0 ± 1.4 and width of 7.7 \pm 0.8 nm.

The as-synthesized NTPs showed a remarkable surface plasmonic property. The fwhm of the LSPR band was as narrow as 91 nm,²⁸ which indicates the high monodispersity of the NTPs (Figure 1b). It should be noted that although branched nanoparticles could also be formed without Au seeds, the extinction spectrum of the produced nanoparticles showed

a broad LSPR band (Figure S1), indicating much less control of the spatial symmetry and a broad size distribution of the branches.²⁹ The optical properties of individual NTPs were obtained using a home-built dark-field scattering microscope (Figure 1c).³⁰ A single NTP exhibited a LSPR peak near 800 nm, which was consistent with the UV-vis-NIR extinction spectrum of NTPs in solutions. The fwhm of a single NTP (77 nm) was similar to that of freshly prepared NTPs (91 nm) in solution, demonstrating the high monodispersity of NTPs prepared by the seed-mediated method. The experimental spectra agreed with the finite difference time domain (FDTD) numerical simulation, which was obtained by solving Maxwell's equations (Figure S2). In addition, we simulated the charge density contours of Au NTPs at the plasmonic peak position. The FDTD results suggest the LSPR peak can be attributed to a coupled longitudinal dipole plasmon resonance from four arms (Figure S3).

Surprisingly, the four arms of the NTPs were not distributed in a tetrahedral configuration symmetrically, that is, not the sp³ carbon conformation. Close inspection of the NTPs reveals that most of the NTPs can be sorted into three types, as shown in Figures 2a and S4. Selected area electron diffraction results for different types of NTPs show that all the NTPs are of single-crystalline nature (Figure 2a). For precise confirmation of each branch orientation, we performed tomography TEM for the three types of NTPs. Interestingly, the analysis of the images obtained with different tilting angles proved that various NTP structures (Figures 2a and S5-6) indeed originated from only one type of tetrapod structure (Figures 2b, S5, and S6). The four arms of the NTPs grew toward [101], $[\overline{101}]$, $[01\overline{1}]$, and $[0\overline{11}]$ directions, respectively; all arms grew along $\langle 110 \rangle$ directions with two pairs of perpendicular arms in two perpendicular planes (Figure 2a). The structure has one S_4 and two C_2 axes and belongs to the D_{2d} point group. To our best knowledge, this is the first report of nanoparticles with D_{2d} symmetry. The unique spatial arrangement of the NTPs is attributed to the kinetically controlled growth and the steric hindrance among the arms (vide infra).

On the basis of the high-resolution TEM image and its fast Fourier transform pattern of a NTP with one arm pointing perpendicular to the substrate (Figure 2c and its inset), we built an atomic model structure of the NTP (Figures 2d and S7) where the lateral facets of arms include four {111} facets separated by two {100} facets. Correspondingly, the tip facets include a small {110} facet surrounded by two {100} and two {111} facets. The angles between the six lateral facets of the arm perpendicular to the substrate are in good agreement with those of the atomic model (Figure S8). In addition, the relatively strong Au {111} peak in the powder X-ray diffraction of NTPs is consistent with the presence of relative large areas of Au {111} facets in the proposed atomic model (Figure 2e).

To explore the preferential growth mechanism of arms in the $\langle 110 \rangle$ directions, we first studied the effect of capping agents, HMT and CTAB. According to density functional theory (DFT) simulation results, HMT adsorbed onto Au crystal planes via the binding between one of its N atoms and Au atoms at the top position. (Figure S9). The adsorption energies (ΔE_{ads}) of HMT on different Au crystal planes were similar to that of CTAB reported previously,³¹ i.e. $|\triangle E_{ads}\{110\}| > |\triangle E_{ads}\{100\}| > |\triangle E_{ads}\{111\}|$. This result suggests that both HMT and CTAB thermodynamically hinder the growth toward the $\langle 110 \rangle$ directions.



Figure 2. (a) Three types of NTPs observed by TEM and their corresponding 3D models of NTPs. (b) TEM images of NTPs tilted in the microscope from ca. -45° to $+45^{\circ}$. (c) High-resolution TEM (HRTEM) image of an individual NTP and its fast Fourier transform pattern (inset). The white dotted lines indicate the six faces of the arm. (d) Atomic structural model of a NTP. (e) Powder X-ray diffraction spectrum of the NTPs. The black line is the conventional value of the gold element. All scale bars: 5 nm.

The growth mechanism of NTPs depended on precise kinetic control over an important parameter, namely, the ratio of deposition rate (V_{dep}) to diffusion rate (V_{diff}) , which is crucial for preparing shape-controlled nanoparticles via a seed-mediated approach $^{32-37}$ High V_{dep} represents that the adatoms in the growth solution prefer to grow on the seed planes with high surface free energies. Meanwhile, a high $V_{\rm diff}$ indicates a fast rate of the deposited atoms diffusing from the high-energy planes to the low-energy planes. In the present study, we used near rhombicuboctahedron Au seeds, on which CTAB preferred to adsorb on the $\{100\}$ and $\{110\}$ facets. The corners with $\{111\}$ facets have the highest surface free energy as a result of the lowest packing density of CTAB. {110} edge facets are relatively more reactive than {100} side facets because of smaller coverage of the capping agent.³⁸ In the case of a fairly slow reduction rate $(V_{\text{diff}} \gg V_{\text{dep}})$, the majority of deposited atoms will diffuse from the corners to edges and then sides. Cuboctahedrons or spheres should be formed resulting from the growth toward $\langle 110 \rangle$ and $\langle 100 \rangle$ orientations, as favored by thermodynamics (Scheme 1a). In the other case of an ultrafast reduction rate ($V_{\rm dep}\gg V_{\rm diff}$), there is negligible diffusion of adatoms which deposited on the {111} corners, resulting in a kinetic product of octopods with



eight arms growing along $\langle 111 \rangle$ directions (Scheme 1c). For a moderate reduction rate, V_{dep} is slightly greater than V_{diff} (Scheme 1b); the combination of effects of the direct deposition of atoms on $\{110\}$ and the diffusion of adatoms from $\{111\}$ to $\{110\}$ facets can lead to the preferential growth in the $\langle 110 \rangle$ directions, that is, on the edge facets.

There are 12 total {110} facets on the rhombicuboctahedron seed. For a moderate $V_{\rm dep}$ that is comparable with $V_{\rm diff}$ the limited number of Au⁰ atoms available for the edge facets can cause the asymmetric growth. In the present case, 4 out of 12 {110} facets have a faster deposition rate compared to others, resulting in the growth of the four arms. The spatial distribution of the arms is determined by the steric hindrance and electrostatic repulsion from the charge of the capping agents, i.e., CTAB. To maximize the sum of angles (or distances) among the four arms, the conformation should possess the lowest steric hindrance and the highest symmetry as compared to other conformations, which is supported by theoretical calculations (Figure S10). In summary, the kinetic parameters, such as the reduction rate, V_{dep} , and V_{diff} , play key roles in controlling the number and spatial arrangement of the arms.

The ratio of V_{dep} to V_{diff} can be controlled by adjusting the amount of seeds and HAuCl₄ or the rate of reduction of HAuCl₄. To understand the growth mechanism, by increasing of the Au seed solution from 1-fold (5.0 μ L, the optimal condition) to 4-fold without changing other experimental parameters, a series of monodisperse NTPs with aspect ratios from 3.1 to 1.7 and arm widths from 9.1 to 6.8 nm was obtained (Figure 3 and Table S1). Further increasing the



Figure 3. (a) Extinction spectra of NTPs using different amounts of seed solution from 2.5 to 50 μ L mixed with the growth solution. Right-top corner: the corresponding picture of the NTP solutions. TEM images of the synthesized NTPs with (b) 2.5 μ L, (c) 5.0 μ L, (d) 10 μ L, and (e) 50 μ L of seed solutions. Scale bars: 50 nm.

volume of the seed solution to 20 fold can significantly reduce V_{dep} and yielded small Au spheres with an average size of 7.0 nm, a thermodynamically stable product. These results also illustrate that the aspect ratio and LSPR wavelength of NTPs can be regulated by tuning the seed/HAuCl₄ ratio, without altering the monodispersity of NTPs as indicated by their narrow peak widths in Figure 3a. Additionally, there was a linear correlation between the aspect ratio and the LSPR wavelength of NTPs (Figure S11). The FDTD simulation results of Au NTPs also show the LSPR peak red-shifted with the increase of arm length, which agreed quite well with the plasmon hybridization theory (Figure S12).^{39,40}

To further increase V_{dep} , we replaced HMT with 1methylpyrrolidine, which can reduce HAuCl₄ to Au⁰ with a much faster rate (Figure S13). Interestingly, instead of NTPs, single-crystalline Au nanooctopods with eight arms were obtained in our previous work.⁴¹ The HRTEM image of nanooctopods shows the eight arms toward the $\langle 111 \rangle$ directions (Figure S14), which is in agreement with the condition for $V_{dep} \gg V_{diff}$ of the growth mechanism (Scheme 1c).

It has been reported that branched Au nanoparticles are often unstable and tend to reshape their morphology,⁴² which consequently changes their plasmonic properties and greatly restricts their potential bioapplications. The as-synthesized NTPs displayed poor stability at room temperature, resulting in quick changes of their morphology and corresponding LSPR peak in less than a few hours (Figure S15a). To address this issue, we developed a PEGylation method to improve the stability for their applications. Upon addition of monomethoxy-poly(ethylene glycol)-thoil (mPEG-SH), the PEGylated NTPs were obtained by forming Au-S bonds. The LSPR of PEGylated NTPs showed ignorable peak shifts at room temperature for a month (Figure S15b) or at 75 °C for 30 min (Figure S16). Therefore, those results indicate that the PEGylation of NTPs can significantly improve their thermal and colloidal stability, which is important for their practical applications.

The NTPs with a strong LSPR band in the NIR region are promising for photoacoustic imaging and photothermal therapy, because NIR irradiation with strong tissue-penetrative ability is widely applied for deep tissue imaging or photothermal therapy to ablate tumors. As a result, it is worthwhile to assess the multifunctionality of PEGylated NTPs, i.e. their photothermal conversion efficiency and photoacoustic properties. Aqueous solutions of PEGylated NTPs with a constant optical density at 808 nm (OD_{808nm}) of 1.0 were subjected to 808 nm laser with power densities from 0.50 to 2.0 W/cm². The temperature of the solutions shows an obvious laserpower dependence (Figure 4a). Additionally, PEGylated NTPs with different optical densities (ODs) from 0.1 to 1.0 were exposed to 808 nm laser irradiation with a constant power density of 1.0 W/cm² (Figure 4b). These results indicate the



Figure 4. (a) Temperature variations of PEGylated NTP solutions $(OD_{808nm}, 1.0)$ upon laser irradiation with different intensities (808 nm, 0.50–2.0 W/cm²). (b) Temperature variations of PEGylated NTP solutions with different optical densities $(OD_{808nm}, 0.10-1.0)$ upon laser irradiation (808 nm, 1.0 W/cm²). (c) Photoacoustic signal amplitude of NTPs plotted with different optical densities. (d) Photoacoustic imaging pictures of NTPs with different optical densities.

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solution temperatures increased with their optical densities and laser intensities. The photothermal conversion of NTPs shows a maximum efficiency up to 55.2% (Table S2).^{43,44} In addition, the NTPs displayed a strong photoacoustic signal with a linear dependence of their optical densities at 808 nm (Figure 4c and 4d). The result suggests that the NTPs are a promising photoacoustic contrast agent. It is worth pointing out that there were not obvious shifts of their LSPR peaks after both photothermal conversion and photoacoustic property measurements, suggesting the excellent stability of PEGylated NTPs without deformation.

In conclusion, monodisperse NTPs with tunable arm lengths were synthesized by a seed-mediated growth method with high yields. The NTPs have a novel D_{2d} symmetry with four arms elongated in four (110) directions. The growth mechanism of the NTPs relies on the delicate kinetic control of the deposition and diffusion rates of adatoms. The tunable arm lengths of the NTPs makes it possible to control their longitudinal plasmonic resonance properties. PEGylated NTPs exhibited excellent thermal stabilities, high photothermal conversion efficiencies (up to 55.2%), and strong photoacoustic responses. These distinctive features of NTPs make them highly promising as a multifunctional theranostic agent for both photoacoustic imaging and image-guided photo-thermal cancer therapy.

ASSOCIATED CONTENT

S Supporting Information

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Materials, methods, Tables S1 and S2, and Figures S1–S16 (PDF)

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Notes

The authors declare no competing financial interest.

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