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Metal-organic Frameworks for Preserving Functionality of Plasmonic Nanosensors

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Abstract

Preserving the functionality of nanosensors is critical for their reliable performance under harsh environmental conditions. Biofunctionalized plasmonic nanostructures are an important class of bionanoconjugates for biosensing, bioimaging and nanotherapeutics. Plasmonic nanostructures and biomolecules exhibit poor thermal stability over time. Here, we report a class of metal-organic framework, zeolitic imidazolate framework-8 (ZIF-8), as a protective coating for preserving plasmonic nanostructures and plasmonic bionanoconjugates at elevated temperature. Gold nanobipyramids (AuNBPs) with sharp tips are attractive plasmonic nanotransducers with high sensitivity but are prone to structural change and loss of sensitivity. This work reports the first observation that ZIF-8 can preserve the structure of AuNBPs, and corresponding strong electromagnetic field enhancement and high refractive index sensitivity. In addition, ZIF-8 coating enables nearly 100% retention of biorecognition capability of antibodies immobilized on the AuNBP surface after exposure to 60°C for 48 hours. The efficacy, versatility, and facile implementation of ZIF-8 coating offer great promise for the preservation of nanosensors.

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Competing Financial Interests

The authors declare no competing financial interests.

Graphical Abstract

Keywords

nanosensors; metal-organic framework; zeolitic imidazolate framework-8; gold nanobipyramid; bionanoconjugates

Introduction

Preserving the structure and functionality of nanostructures and bionanoconjugates used in nanosensors is critical for their reliable performance under harsh environmental conditions.^{1–3} Bionanoconjugates comprised of biomolecules and functional nanostructures with synergistic properties are a unique class of materials with promise in a wide range of applications, including biosensing, biocatalysis, nanomedicine, and bioremediation.^{4–5} The limited stability of these hybrid materials often leads to the degradation of their functionalities under harsh environmental conditions.^{5–7} For example, plasmonic nanostructures with sharp tips, such as gold nanobipyramids and nanostars, can provide high sensitivity due to a strong enhancement of electromagnetic fields around their sharp tips.^{8–9} However, atoms at the tips tend to undergo structural rearrangements to minimize surface energy, resulting in the poor thermal stability and long-term stability at ambient temperature.¹⁰ Additionally, the analytical validity of biosensors relies on stable biorecognition elements. These biorecognition elements, such as antibodies, are prone to denature when stored at ambient temperature.¹¹ These limitations present a significant barrier in the applications of plasmonic sensors for chemical and biological diagnostics. Therefore, there is a critical demand to develop a simple, cost-effective, and biocompatible approach to preserve the structure and functionality of nanoparticles and bionanoconjugates.

Plasmonic biosensors promise simple, cost-effective, and sensitive biomolecular diagnostics in resource-limited settings.^{12–13} Localized surface plasmon resonance (LSPR) occurs from collective oscillation of conduction electrons in noble metal nanoparticles in response to the oscillating electric field of incident electromagnetic (EM) radiation.^{14–15} The LSPR wavelength is highly sensitive to the local refractive index changes of surrounding environment induced by events such as molecular binding. Facile and label-free measurements of molecular binding events can be accomplished by measuring

the extinction spectrum of plasmonic nanostructures.^{16–17} These factors, combined with miniaturization of readout devices, render LSPR biosensors an attractive option for point-of-care (POC) biosensing. In addition, EM field enhancement at or near the surface of metallic nanoparticles provides large enhancements for Raman scattering that forms the molecular vibrational fingerprint of analytes in close proximity to the nanoparticles.¹⁸ Known as surface enhanced Raman spectroscopy (SERS), this technique provides a highly sensitive analytical tool for the quantitative and qualitative measurements of trace amounts of analytes in close proximity to plasmonic nanostructures. The size, geometry, and composition of plasmonic nanostructures largely determine their refractive index sensitivity (RIS) and near-field EM field enhancement.^{19–22}

Zeolitic imidazolate framework-8 (ZIF-8) encapsulated metal nanoparticles are attractive nanocomposites for various applications, such as catalysis and sensing, due to the combined properties of nanometals and metal-organic framework (MOF).^{23–27} Capping agents, such as cetyltrimethylammonium bromide (CTAB), on metal nanoparticle surfaces facilitate the interaction between metals surface and ZIF-8 precursor.^{27–28} Inspired by the natural biomineralization processes in living organisms, MOF encapsulation has been reported to provide structural and chemical protection to enzyme, antibodies, anaerobic bacteria and viruses.^{7, 29–35} Additionally, MOF coating around nanostructures can enhance sensing performance, such as stability and selectivity.^{27, 36–37} ZIF-8 is particularly favored as a class of MOFs due to its large surface area, biocompatibility, excellent thermal and chemical stability, and ease of removal. MOF crystals grown around biomolecules form a stable and tight encapsulation layer, thus preventing their structural changes and denaturation. ZIF-8 growth occurs spontaneously around biomolecules owing to their strong noncovalent interactions with imidazole and inorganic cations. Based on these previous studies, we hypothesize that ZIF-8 can preserve the structure and properties of nanostructures that are not thermally stable. The ZIF-8 coating can provide the tight encapsulation to restrain the rearrangement of atoms in nanostructures and biomacromolecules, thus preserving the functionality of the plasmonic nanosensors. The main advantage of ZIF-8 coating is the superior preservation efficiency compared to other materials, including organosiloxane, CaCO_3 and SiO_2 , reported previously.^{6, 30}

This paper reports ZIF-8 as a versatile exoskeleton can prevent the structural change of gold nanobipyramids (AuNBPs) and preserve the structure and functionality of bionanoconjugates under harsh environmental condition, such as high temperature. In resource-limited settings, the temperature spikes above 40°C might occur during transport and storage of plasmonic nanosensors. The high temperature can cause structural change of AuNBPs and denaturation of biorecognition elements in chemical and biological sensors. This work reports the first observation that ZIF-8 coating can preserve the structure of AuNBPs and corresponding EM field enhancement and RIS at elevated temperatures and for long-term storage. Freshly prepared AuNBPs and preserved AuNBPs, after harsh treatments and ZIF-8 removal, provide the same sensitivity in chemical and biological detection based on SERS and LSPR. In contrast, the AuNBPs with truncated tips have much lower sensitivity. In addition, ZIF-8 coating provides nearly 100% retention of biorecognition capability of antibodies after exposure to 60°C for 48 hours.

Results and Discussion

AuNBPs were synthesized using a previously reported seed mediated method.³⁸ AuNBPs undergo tip rounding to reduce the surface energy as the mobility of surface atoms increase under prolonged exposure to elevated temperatures, as shown in the Figure 1a. Figure 1b shows a transmission electron microscope (TEM) image of as synthesized AuNBPs with 117 ± 4 nm in length, 33 ± 2 nm in center width, and sharp tips with the radius of curvature 5 ± 1 nm, noted as S-AuNBPs. After immobilizing the S-AuNBPs on substrates, we performed temperature-accelerated stability tests by exposing the samples to a series of thermal treatments, including 125°C or 60°C for different durations of time. Thermally induced structural rearrangement of S-AuNBP results in a shortened structure with truncated tips, denoted as truncated AuNBPs (T-AuNBPs). TEM images show the morphology of as-synthesized S-AuNBPs and T-AuNBPs induced by 125°C for 12 hours (Figure 1b). Corresponding dimensional analysis of AuNBPs shows the length of S-AuNBP reduces to 78 ± 4 nm by ~33% (Figure 1c, number of AuNBPs=100). In contrast, the width of both structures remains similar. The radius of curvature of T-AuNBPs is 12 ± 1 nm, significantly higher than that of S-AuNBPs, indicating that length reduction is a result of tip truncation with a smoothened curvature (Figure 1c). The aspect ratio (length/width) of S-AuNBPs changes from 3.5 to 2.3. The extinction spectrum of S-AuNBPs exhibits two distinct bands with wavelength at 525 nm and 751 nm, corresponding to the transverse and longitudinal oscillation of electrons with incident EM field, respectively. The longitudinal LSPR (LLSPR) band has higher refractive index sensitivity than the transverse LSPR (TLSPR) band.

Due to the 125°C treatment, the extinction spectrum of S-AuNBPs after truncation exhibits a significant blue shift of 78 nm in the LLSPR wavelength from 751 nm to 673 nm and a smaller blue shift of 6 nm in the TLSPR wavelength from 524 nm to 518 nm (Figure 1d). Hereafter, we use the LLSPR of AuNBPs for analysis due to its higher sensitivity. As expected, exposure to milder condition of thermal treatment at 60°C produces a blue shift in the LLSPR wavelength of ~13 nm in the first 24 hours and then with a slower rate of 6 nm blue shift per day (Figure 1e and 1f). The cumulative LLSPR blue shift of S-AuNBPs under 60°C after 13 days is similar as that under 125°C after 12 hours. The prolonged thermal reshaping of S-AuNBPs under milder conditions is further confirmed by TEM images of AuNBPs showing moderately truncated tips following the storage at room temperature (RT) for 150 days. (Figure S1a). Corresponding dimensional analysis shows that the length of S-AuNBPs reduces to 103 ± 3 nm by ~12% while the width remains similar (Figure S1b). The radius of curvature of the AuNBPs increased to 7 ± 1 nm, significantly higher than that of S-AuNBPs but less than T-AuNBPs exposed to 125°C for 12 hours (Figure S1b). Room temperature storage for 150 days produces a blue shift of ~27 nm in the LLSPR wavelength (Figure S1c). These results confirm that the tips of S-AuNBPs become truncated and the structural change results in a blue shift in the LSPR wavelength after long-term storage under RT or after exposure to a high temperature for a short time.

To preserve the structure of S-AuNBPs, we synthesize ZIF-8 nanocrystals around the S-AuNBPs to suppress the surface diffusion kinetics of the S-AuNBPs. The formation of ZIF-8 exoskeletons involves the immersion of S-AuNBPs on substrates to an aqueous

solution composed of zinc nitrate (8 mM), 2-methylimidazole (440 mM) and CTAB (0.04 mM) for 3 hours (Figure 2a). The CTAB as an additive facilitates the nucleation and growth of ZIF-8 crystals on metal surfaces, as previously demonstrated.^{28, 39} TEM images show a substantial nucleation and growth of ZIF-8 encapsulant around S-AuNBPs after 5 minutes of immersion in the precursor solution (Figure 2b). The ZIF-8 exoskeleton continues to grow and results in the formation of connected ZIF-8 coating around the S-AuNBPs following 30 minutes of growth. Time evolution of ZIF-8 crystallization around S-AuNBPs on glass slides is revealed by measuring the extinction spectra of the S-AuNBPs immersed in the ZIF-8 precursor solution over time (Figure 2c). The LLSPR wavelength of the S-AuNBPs after immediately placing in the ZIF-8 precursor solution is measured to be 894 nm. Encapsulation process results in a gradual red shift in the LLSPR wavelength of the S-AuNBPs with initial rapid growth and gradually plateau over time (Figure 2d). Figure 2e shows XRD pattern of ZIF-8 crystals after the growth for 3 hours. All the peaks are in agreement with the typical structure of ZIF-8 reported previously.^{40–41}

Next, we demonstrate that ZIF-8 exoskeleton can prevent S-AuNBPs from reshaping by exposing the ZIF-8 encapsulated S-AuNBPs under 125°C for 12 hours. The ZIF-8 coating results in a red shift of 202 ± 3 nm in LLSPR wavelength of the S-AuNBPs (Figure 3a). The measured extinction spectra show 7 ± 1 nm blue shift in the LLSPR wavelength of ZIF-8 coated S-AuNBPs due to slight dehydration during the thermal treatment (Figure 3a). Next, we removed ZIF-8 coating by immersing the S-AuNBPs chips in ZIF-8 dissociation buffer composed of 0.2 M phosphate buffer with 2 mM ethylenediaminetetraacetic acid (EDTA) for two minutes followed by rinsing with deionized water. The LLSPR wavelength of the S-AuNBPs exhibits 196 ± 2 nm blue shift due to ZIF-8 removal (Figure 3a). An additional round of incubation with the dissociation buffer does not result in further blue shift, indicating the complete removal of the ZIF-8 coating. The LLSPR wavelength shows 2 ± 1 nm blue shift compared to the original wavelength of the S-AuNBPs, suggesting the preservation of the structure (Figure 3b). The intensity and the full width at half maximum (FWHM) of the extinction spectra depend on the density and distribution of AuNBPs on the substrates. We observed little change in the intensity and FWHM of AuNBPs before ZIF-8 coating and after removing the coating, suggesting that the ZIF-8 coating and removal does not affect the distribution of AuNBPs on glass substrates. The coating and removal of ZIF-8 are further confirmed with surface enhanced Raman spectroscopy (SERS). Raman bands at 685 cm^{-1} , 1146 cm^{-1} and 1460 cm^{-1} correspond to the imidazolium ring puckering, C5-N stretching, and antisymmetric methyl bending of ZIF-8, respectively (Figure 3c).⁴²⁻⁴⁴ The inset image in Figure 2h shows a TEM image of the S-AuNBPs after thermal treatment and ZIF-8 removal and corresponding dimensional analysis of the preserved S-AuNBPs. The dimension of S-AuNBPs preserved with ZIF-8 protective coating does not exhibit any changes compared to the original nanostructures following thermal treatment at 125°C for 12 hours (Figure 3d). It is important to note that CTAB plays an important role in ZIF-8 coating and resultant preservation. Without CTAB added in the ZIF-8 precursor solution, S-AuNBPs show a blue shift of ~ 26 nm after exposure to 125 °C for 12 hours, suggesting decreased preservation of S-AuNBPs (Figure S2a, S2b). As shown in the literature²⁷, the concentration of CTAB could be optimized to eliminate the self-nucleation of ZIF-8 observed in the TEM images (Figure 2b). Decreasing synthesis time of the ZIF-8 might

also decrease the preservation efficiency, possibly due to the lower crystallinity (Figure S2c).⁴⁵ These results suggest that ZIF-8 can fully preserve S-AuBNPs structure under high temperature. Rapid coating and on-demand removal of ZIF-8 exoskeleton around nanostructures are also demonstrated.

In SERS based sensing applications, the intensity enhancement of Raman scattering is largely determined by the strong EM field near the plasmonic nanostructures.^{46–49} AuBNPs are among a class of anisotropic nanostructures with sharp tips where electromagnetic (EM) field is concentrated to generate EM “hot spots”.^{50–51} Theoretical calculations indicate that AuBNPs exhibit a much stronger EM field enhancement than other nanostructures including nanorods and nanospheres due to the presence of sharp tips.⁵² We investigated the EM field enhancement difference between S- AuBNPs and T- AuBNPs with computational and experimental approaches. The finite-difference time-domain (FDTD) simulation calculates the distribution of EM field intensity around S-AuNBP and T-AuNBP with the dimension measured from TEM images. The calculated EM field intensity at the excitation wavelength of 780 nm averaged from the area of 30 nm away from the surface of S-AuNBP is 3.6 times larger than that of T-AuNBP (Figure 4a).

We then measured and compared the SERS performance of S-AuNBP and T-AuNBP using 4-aminothiophenol (*p*-ATP) as a model Raman reporter. Following a previously established approach, S-AuBNPs uniformly adsorbed on a filter paper serve as a SERS substrate.^{53–54} Extinction spectrum of S-AuBNPs on paper shows a symmetrical longitudinal band, confirming the uniform distribution of the S-AuBNPs on the paper substrate (Figure S3a). The SEM image of AuBNPs on the paper substrate reveals uniform distribution of individual AuBNPs with little aggregations (Figure S3b). This suggests the SERS enhancement primarily results from the EM hotspots at the tip of individual AuBNPs. We exposed S-AuNBP paper to 125°C for 12 hours to obtain T-AuNBP paper for SERS performance comparison. To validate the efficiency of the ZIF-8 as a protective coating, the SERS spectra were collected from the S-AuNBP paper preserved by the ZIF-8. Following the same approach discussed above, we immersed an S-AuNBP paper in the ZIF-8 precursor solution for encapsulation, and then exposed the paper to the same thermal treatment, followed by the removal of ZIF-8 using the dissociation buffer. Figure 4b and 4c show the SERS spectra of *p*-ATP adsorbed on the S-AuNBP and T-AuNBP after exposure to varying concentrations of *p*-ATP solution from 100 μ M down to 1 nM. The prominent peaks observed at 1140 cm^{-1} , 1390 cm^{-1} , 1436 cm^{-1} , 1574 cm^{-1} correspond to the fundamental benzene ring vibrations (ν_{9b} , ν_3 , ν_{19b} , and ν_{8b} , respectively), while the peak at 1072 cm^{-1} corresponds to CS stretching (a_1 mode).⁵⁵ As expected, the SERS intensity decreases monotonically with the decrease in the *p*-ATP concentrations. To evaluate the effect of ZIF-8 coating on the SERS intensity, we collected SERS spectra of *p*-ATP from the S-AuNBP paper with and without ZIF-8 coating. The SERS intensity of *p*-ATP collected from the S-AuNBP paper is 3.2 times higher than that from the ZIF-8 coated paper (Figure S7c). The decrease in the SERS intensity of the ZIF-8 coated samples might result from less active sites on the S-AuNBP surface for *p*-ATP enhancement.

Figure 4d shows the SERS spectra of *p*-ATP collected from the T-AuNBP, S-AuNBP and preserved S-AuNBP papers after exposure to 100 μ M *p*-ATP solutions. The SERS

intensities of 1141 cm^{-1} Raman band measured from S-AuNBP and preserved S-AuNBP papers are comparable and are ~ 10 fold higher than that of T-AuNBP paper. For 780 nm excitation, the Stokes-shift wavelength corresponding to 1141 cm^{-1} Raman band is at $\sim 856\text{ nm}$. The simulated distribution of EM field intensity around S-AuNBP at 856 nm is 2.7 times higher than that of T-AuNBP (Figure S3c). The theoretical SERS enhancement is approximated with the product of the gain in the average EM intensity enhancement of the incident and Raman scattered light ($(|E_{780}|^2|E_{856}|^2)$). The calculated SERS enhancement for S-AuNBP is ~ 9.7 times larger than that of T-AuNBP, which agrees well with the higher SERS enhancement of S-AuNBP in the experimental results. The S-AuNBP and preserved S-AuNBP papers allow for the detection of *p*-ATP at 10 nM as the low limit of detection (LOD: signal to noise ratio >3) (Figure 4e). In contrast, the Raman bands of *p*-ATP collected from the T-AuNBP paper at 10 nM and 100 nM are not distinguishable compared to the reference sample without exposure to *p*-ATP. In the reference spectrum collected from AuNBP without *p*-ATP, the Raman bands at 758 cm^{-1} and 1442 cm^{-1} (marked with stars) correspond to CH_3 rock and CH_2 bend of CTAB.⁵⁶ Figure 4f shows SERS intensity of 1141 cm^{-1} Raman band collected from the T-AuNBP, S-AuNBP and preserved S-AuNBP papers corresponding to the concentrations of *p*-ATP solutions from 1 nM to $10\text{ }\mu\text{M}$. The SERS intensity from S-AuNBP and preserved S-AuNBP papers follows the same within standard deviation and is higher than that from T-AuNBP paper at all the concentrations. The low limit of *p*-ATP detection with S-AuNBP paper is two orders of magnitude lower than that with T-AuNBP paper ($1\text{ }\mu\text{M}$). The concentration of *p*-ATP (C) and the SERS intensity (I) from T-AuNBP, S-AuNBP and preserved S-AuNBP following the relationship of $\text{Log } C = 2.5 \text{ Log } I - 2.9$, $\text{Log } C = 2.4 \text{ Log } I - 5.1$, $\text{Log } C = 2.3 \text{ Log } I - 4.6$ with $R^2 = 0.98$, respectively. Additionally, the SERS intensity collected from two batches shows small variations (Figure S3e, S3f). These results suggest that S-AuNBPs as SERS nanotransducers provide much higher sensitivity than T-AuNBPs. The ZIF-8 exoskeleton can preserve the structure of S-AuNBPs used in SERS substrates and the complete removal of ZIF-8 coating does not affect the sensitivity of SERS signals.

Previous work have shown that shapes and sizes of gold nanocrystals largely affect their refractive index sensitivity (RIS), an important design parameter for LSPR-based sensors.^{19, 57–58} Here, we directly compare the refractive index sensitivity of T-AuNBPs, S-AuNBPs and preserved S-AuNBPs. We employ sucrose aqueous solutions as surrounding medium owing to their well-defined refractive indexes at different concentrations (Figure S4).⁵⁹ Figure 5a and 5b show the extinction spectra of S-AuNBPs and T-AuNBPs after exposing to the concentration of sucrose solutions from 0% to $42\text{ w/v}\%$ to result in a linear increase in the refractive index of surrounding media from 1.3333 to 1.4036 . The LSPR wavelength exhibits gradual red shifts with the increase in the refractive index (Figure 5c). The calculated RIS of the S-AuNBPs is 353 nm/RIU , which is 29% higher than that of T-AuNBPs (274 nm/RIU). We also prepared ZIF-8 preserved S-AuNBPs as discussed above. The figure of merit, the refractive index sensitivity divided by the full width at half-maximum of the extinction peak, of S-AuNBPs is 4.3 , $\sim 16\%$ higher than that of T-AuNBPs. The LSPR wavelength of the preserved S-AuNBPs follows the same as that of the S-AuNBPs with RIS of 352 nm/RIU , further confirming the effective preservation of S-AuNBPs with the ZIF-8 coating.

We reveal the shape effect of AuNBPs on the sensitivity of LSPR biosensors using human IgG and anti-human IgG as a model pair of biorecognition element and target protein, respectively. First, we functionalized the S-AuNBPs and T-AuNBPs with Protein A (PA) to conjugate the IgG with a preferable orientation, facilitating the interaction between antigen-binding fragment (Fab) and the target protein.⁶⁰ Figure 5d and 5e show the extinction spectra of S-AuNBPs and T-AuNBPs, following each step of functionalization. The LSPR wavelength of the AuNBPs exhibits red shift after each step due to the increase in the refractive index (Figure 5f). The LSPR wavelength shifts of the S-AuNBPs corresponding to the binding of PA, IgG, and anti-IgG are 27.5 ± 0.8 nm, 17.7 ± 0.9 nm, and 17.8 ± 0.6 nm, respectively. In contrast, the LSPR wavelength shifts of the T-AuNBPs corresponding to the binding of PA, IgG, and anti-IgG are 17.6 ± 0.5 nm, 14.2 ± 0.7 , and 12.7 ± 0.6 nm, respectively. The LSPR wavelength of the S-AuNBPs exhibits higher shift than that of the T-AuNBPs for each functionalization step, which agrees well with the higher RIS of the S-AuNBPs. Additionally, we tested the selectivity of the biosensor to anti-human IgG by exposing AuNBP-human IgG to anti-rabbit IgG of 10 $\mu\text{g/ml}$, an interfering protein. Little shift from the anti-rabbit IgG confirms the selectivity (Figure S5a). We also tested the sensitivity and specificity of the biosensor with complex serum samples, containing high concentrations of various proteins. A red shift of ~ 22 nm results from anti-human IgG of 10 $\mu\text{g/mL}$ in 10% bovine serum and ~ 3 nm results from the 10% bovine serum without anti-human IgG, which confirm the performance of the biosensors in complex samples (Figure S5b, S5c).

We demonstrate that the ZIF-8 exoskeleton can simultaneously preserve the S-AuNBP structure and the functionality of the biorecognition elements for LSPR-based biosensing. Figure 6a shows the schematic illustration of ZIF-8 coating around the S-AuNBP functionalized with PA and IgG, and ZIF-8 removal on demand for anti-IgG detection. The functionalization of the S-AuNBP with PA and IgG follows the same as the description above. The ZIF-8 coating involves the immersion of the biofunctionalized S-AuNBPs on glass slides in the ZIF-8 precursor solution composed of zinc nitrate (8 mM) and 2-methylimidazole (440 mM) for 3 hours. No CTAB is added to the ZIF-8 precursor solution as biomolecules are known to facilitate the nucleation and growth of ZIF-8.³⁰ Time evolution of extinction spectra of AuNBP-PA-IgG in the ZIF-8 precursor solution shows gradual red shifts in the LSPR wavelength of the AuNBP up to ~ 43 nm at 84 minutes (Figure 6b and 6c). TEM images show a substantial nucleation and growth of ZIF-8 encapsulant around AuNBP-PA-IgG after 5 minutes of immersion in the precursor solution (Figure 6d). Figure 7a shows the extinction spectra of the S-AuNBPs following each step shown in the schematic in the Figure 6a. Figure 7b shows the LSPR wavelength of the S-AuNBPs to reveal the incremental LSPR shift induced by each step. The steps 1-6 represent the fresh S-AuNBPs, AuNBP-PA-IgG, ZIF-8 coated AuNBP-PA-IgG (AuNBP-PA-IgG@ZIF-8), AuNBP-PA-IgG@ZIF-8 after the thermal treatment, AuNBP-PA-IgG after the ZIF-8 removal, and AuNBP-PA-IgG after anti-IgG capture, respectively. The LSPR wavelength of the AuNBP-PA-IgG exhibits a red shift of 157 ± 2 nm following the ZIF-8 coating. Thermal stability tests involve the exposure of AuNBP-PA-IgG@ZIF-8 to 60°C for 48 hours. The thermal treatment induces a blue shift of ~ 7 nm in the LSPR wavelength of AuNBP-PA-IgG@ZIF-8 due to dehydration of the ZIF-8. Following the removal of

ZIF-8, the LLSPR wavelength of AuNBP-PA-IgG exhibits a blue shift of ~151 nm and returns to the original wavelength of the AuNBP-PA-IgG, confirming the complete removal of ZIF-8. Subsequently, the binding of the anti-IgG of 10 $\mu\text{g/mL}$ in phosphate-buffered saline (PBS) results in a red shift of 17.5 ± 0.7 nm. For comparison, extinction spectra were collected from the AuNBP-PA-IgG without the ZIF-8 protection after the thermal treatment and the anti-IgG binding (Figure 7c). After the thermal treatment, the LLSPR wavelength of AuNBP-PA-IgG exhibits a blue shift of 17.4 ± 0.5 nm, largely due to the slight truncation of the AuNBPs, confirmed by the TEM image (Figure S6). Upon the binding of the anti-IgG, the LLSPR wavelength of AuNBP-PA-IgG shows a red shift of 4.9 ± 0.3 nm without the ZIF-8 protection. The LLSPR wavelength shifts induced by each step in the biosensing experiments are summarized in a table for clarification (Table S1). The LLSPR wavelength shifts due to the anti-IgG binding are normalized against that measured from the freshly prepared AuNBP-PA-IgG (17.8 ± 0.6 nm) to derive the percentage retention in biorecognition capability (Figure 7d). The results show 98% biorecognition retention of the ZIF-8 protected AuNBP-PA-IgG after exposure to 60°C for 48 hours, compared to a retention of only 28% for the unprotected AuNBP-PA-IgG (Figure 7d). The significant decrease in the biorecognition retention of the unprotected AuNBP-PA-IgG is attributed to the denaturation of IgG at 60°C. The retention rate of the biorecognition capability with the ZIF-8 demonstrated here is much higher than the reported rate of 80% in previous studies under the same thermal condition.¹¹ The higher retention is likely due to the better encapsulation by the ZIF-8, evidenced by the higher LSPR wavelength shift of ~157 nm, resulted from the growth of the ZIF, compared to ~65 nm in previous reports. Collectively, we show that the ZIF-8 exoskeleton can preserve the structure and functionality of the AuNBP-PA-IgG bionanoconjugates. The preservation capability of ZIF-8 might originate from its stable structure at the interface and the strong interaction between the ZIF-8, biomolecules and nanostructures at high temperature, thereby preventing the formation of new free surfaces where atoms are free to diffuse and rearrange.

Conclusions

We show that AuNBPs undergo structural changes, including the truncation of sharp tips and reduced aspect ratio, at elevated temperatures or after long-time storage at ambient temperature. Such structural changes decrease the near-field EM enhancement and RIS of the AuNBPs. In addition, the biomolecules immobilized on the AuNBPs lose the functionality upon exposure to high temperature. We demonstrate that ZIF-8 as an exoskeleton can fully preserve the sharp tips of AuNBPs with retained sensitivity for SERS spectroscopy. The ZIF-8 can also simultaneously preserve the structure and biofunctionality of bionanoconjugates. The retention of biorecognition capability of antibodies immobilized onto the AuNBP surface is nearly 100% after two days of storage at 60 °C. The preservation of nanostructures and antibodies can obviate the need for refrigerated transport and storage, making it suitable for the applications in resource-limited settings. This simple and versatile encapsulation approach can be easily adapted to preserve a broad range of nanostructures and bionanoconjugates for various applications.

Experimental Section

Materials:

Cetyltrimethylammonium bromide (CTAB, 99%), gold (III) chloride trihydrate ($\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$, 99.9%), ascorbic acid (99.0%), silver nitrate (AgNO_3 , 99.0%), sodium borohydride (NaBH_4 , 98%), 8-hydroxyquinoline (8-HQL, 99.0%), poly(sodium-p-styrenesulfonate) (PSS, average M.W. $\sim 1,000,000$), 4-aminothiophenol (*p*-ATP, 97%), and zinc nitrate hexahydrate ($\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, 98%) were purchased from Sigma Aldrich. Nitric Acid (HNO_3 , 70%), hydrogen Peroxide (H_2O_2 , 30%), sulfuric Acid (H_2SO_4 , 95.0 to 98.0 w/w %), phosphate buffered saline (PBS, 10X), ethylenediaminetetraacetic acid (EDTA, >99%), sucrose and sodium hydroxide (NaOH , 97.0%) were purchased from Fisher Chemical. Hexadecyltrimethylammonium chloride (CTAC, 99%), and 2-methylimidazole (99%) were purchased from ACROS Organics. Protein A, human IgG, mouse anti-rabbit IgG, fetal bovine serum, and goat anti-human IgG were purchased from Invitrogen. Type 1 deionized water (18.2 m Ω -cm) was used in all experiments and produced by Sartorius Arium Pro ultrapure water system. The filter paper (Whatman No. 1 grade) used in SERS experiments was purchased from Fisher Chemical.

AuNBPs synthesis:

AuNBPs were synthesized following a seed-mediated method with minor modifications.³⁸ To prepare polycrystalline seeds, 4 mL of HAuCl_4 (0.5 mM) and 72 μL of HNO_3 (250 mM) were mixed into an aqueous solution of 4 mL CTAC (95 mM) at room temperature, followed by rapid injection of 100 μL ice-cold mixture containing 50 mM NaBH_4 and 50 mM NaOH under vigorous stirring at 1000 rpm. The role of NaOH is to regulate the reduction potential of reductants in the seed solution.^{38, 61} After one minute of stirring, 16 μL of citric acid (1 M) was added and the seed solution was aged in an oil bath at 80°C for 4 hours. The color of the seed solution changed from light yellow to bright red. Polycrystalline seeds were stored at room temperature prior to use for AuNBPs growth. AuNBPs growth solution was prepared by adding 36 μL of aqueous AgNO_3 (10 mM) and 80 μL of 8-HQL (400 mM in ethanol) into a mixture of 80 μL of aqueous HAuCl_4 (25 mM) and 8 mL of aqueous CTAB (47mM). Following this, 40 μL of polycrystalline seeds was injected to the growth solution, followed by gentle stirring for ten seconds. The growth solution was then placed in an oil bath at 40°C under stirring at 500 rpm. Following 15 minutes of aging, additional 50 μL of 8-HQL (400 mM in ethanol) was injected and the growth solution was aged for another 30 minutes. The color of growth solution changed from light yellow to magenta. Finally, the growth solution was centrifuged once at 7700 rpm for 30 minutes, and then redispersed in the same volume of water for further use.

AuNBPs-PA-IgG conjugation:

Glass substrates were cleaned in piranha solution (3:1 (v/v) mixture of H_2SO_4 and 30% H_2O_2) followed by extensive rinsing with water. Clean glass substrates were immersed in 0.2 w/v% PSS aqueous solution for 1 hour and rinsed with nanopure water. The PSS-modified glass slides were incubated in AuNBPs solution overnight to achieve uniform adsorption. The AuNBPs coated glass slides were incubated in aqueous PA (10 $\mu\text{g/mL}$) overnight at 4 °C and rinsed with nanopure water. Subsequently, the AuNBP-PA slides were

incubated with human IgG (10 $\mu\text{g/mL}$ in 1X PBS) for 90 minutes, followed by rinsing with 1 ml of 1X PBS and nanopure water. Finally, the AuNBP-PA-IgG slides were incubated with anti-human IgG (10 $\mu\text{g/mL}$) for 90 minutes, followed by rinsing with 1 mL of 1X PBS and nanopure water. A group of AuNBP-PA-IgG slides was prepared with additional steps, including ZIF-8 coating, thermal treatment, and removal of ZIF-8 coating prior to incubation with anti-human IgG.

ZIF-8 growth and removal:

ZIF-8 growth solution was prepared based on a previously reported protocol with modifications.²⁷ Briefly, ZIF-8 growth solution was prepared by mixing 1 mL of aqueous zinc nitrate (24 mM) and 4 μL of CTAB (100 mM) with 2 mL of aqueous 2-methylimidazole (660 mM). The same ZIF-8 growth solution without the addition of CTAB was employed for AuNBP-PA-IgG coated glass slides. The AuNBPs or AuNBP-PA-IgG coated substrates, including glass slides, filter paper and TEM grids, were incubated in the ZIF-8 growth solution for three hours at room temperature. The SEM image of AuNBPs on the glass substrate reveals uniform distribution of individual AuNBPs with little aggregations (Figure S8). ZIF-8 coated glass slides were dried with nitrogen gas while TEM grids and paper were naturally dried in air. ZIF-8 coated AuNBPs on glass and paper substrates were kept at 125°C for 12 hours. ZIF-8 coated AuNBP-PA-IgGs on glass substrates were kept at 60°C for 48 hours. Following the thermal treatment, ZIF-8 coating was removed from AuNBPs or AuNBP-PA-IgG by immersing the substrates in 0.2 M phosphate buffer (pH 5.7) with 2 mM EDTA for two minutes with gentle shaking, followed by rinsing with nanopure water. It is important to note that the final pH of dissociation buffer below 6 and the addition of EDTA ensure the complete removal of the ZIF-8 coating. The pH needs to be optimized according the amount of the ZIF-8 crystals in the sample. A very low pH buffer (pH<5) is not recommended to use for biosensors as it might denature the antibodies. The TEM sample and sensor preparation follow the same orders, starting with AuNBP immobilization on substrates and then ZIF-coating and removal. The aggregation of nanoparticles in TEM images is due to suboptimal adsorption of AuNBPs on the Formvar surface of TEM grids.

Finite-Difference Time-Domain (FDTD) Simulation:

EM field distributions of AuNBPs were calculated using a commercial three-dimensional FDTD software. The absorbing boundary conditions of perfectly matched layer were obtained in different directions. The optical dielectric function of gold is calculated using a Drude–Lorentz dispersion function and the refractive index of the surrounding medium was set to 1 as air in all simulations. Three-dimensional S-AuNBP and T-AuNBP were calculated based on dimensions measured from TEM images. High-resolution simulation was performed at the excitation wavelength of 780 nm and the emission wavelength of 865 nm to derive the spatial map of EM field intensity enhancement.

Surface Enhanced Raman Spectroscopy (SERS):

SERS substrates were prepared by immersing commercially available laboratory paper in AuNBPs solution overnight, followed by rinsing with nanopure water. A group of AuNBP paper was prepared with additional steps, including ZIF-8 coating, thermal treatment, and removal of ZIF-8 coating prior to incubation with *p*-ATP solution. Subsequently, AuNBPs-

coated paper substrates were immersed in various concentrations of *p*-ATP in ethanol from 1 pM to 100 nM for 2 hours and thoroughly rinsed with ethanol. We measured the SERS intensity of *p*-ATP from the sample prepared with different incubation time. Compared to the sample with 2 hour incubation, the sample incubated for 1 hour exhibits similar intensity and the sample incubated for 10 min shows ~80% of the intensity due to high affinity of pATP to gold surface (Figure S7). Raman spectra were collected from three spots within the same substrate to obtain the average. The spectra were measured in the wavelength range of 400 cm⁻¹-1800 cm⁻¹ with exposure time of 1 s.

Characterization:

UV-Vis spectrophotometer (Shimadzu UV-1900) was used to collect extinction spectra of AuNBPs aqueous solution and AuNBPs on glass slides in the range of 400-1100 nm. Growth of ZIF-8 exoskeleton on AuNBPs was monitored with continuous spectra collection with 2 minutes intervals. Transmission electron microscopy (TEM) images were collected with JEOL 1200 EX and AuNBP dimensions were estimated from TEM images using ImageJ. Extinction spectra of AuNBPs on paper were measured using a microspectrophotometer (CRAIC 308PV) attached to a Leica optical microscope (DM4M) with 20X objective in the range of 450-900 nm. SERS spectra were measured using a DXR Raman spectrometer with a 780 nm wavelength diode laser (24 mW) as illumination source.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

S-AuNBP reshaping under high temperature or long-term storage. (a) Schematic illustration of S-AuNBP thermal reshaping. (b) TEM images of as-synthesized AuNBPs with sharp tips (S-AuNBPs) and AuNBPs with truncated tips (T-AuNBPs) after storage at 125°C for 12 hours. (Magnification: 100,000X) (c) Dimension comparison of S-AuNBPs and T-AuNBPs, measured from (b). (d) Extinction spectra of S-AuNBPs before and after storage at 125°C for 12 hours. (e) Time evolution of extinction spectra and (f) corresponding LLSR wavelength shift of S-AuNBPs after storage at 60°C for 14 days. Error bars represent standard deviations from three independent samples.

Figure 2.

ZIF-8 coating of S-AuNBP structure. (a) Schematic illustration of S-AuNBP encapsulation with ZIF-8 exoskeleton. (b) TEM images of S-AuNBPs following 5 and 30 minutes of ZIF-8 coating, respectively. (Magnification: 100,000X) (c) Time evolution of the extinction spectra showing the growth of ZIF-8 around S-AuNBPs and (d) corresponding LLSPR wavelength shift. (e) XRD pattern of ZIF-8 crystals.

Figure 3.

Preservation of S-AuNBP structure with ZIF-8. (a) Extinction spectra of S-AuNBPs, after ZIF-8 coating, storage at 125°C for 12 hours, and ZIF-8 removal, and (b) corresponding LLSPR wavelength shift following each step (Error bars represent standard deviations from three independent samples), and (c) corresponding Raman spectra following each step. (d) Dimensions of S-AuNBPs and ZIF-8 preserved S-AuNBPs. Inset: TEM image of the ZIF-8 preserved S-AuNBPs. (Magnification: 100,000X)

Figure 4.

SERS performance of S-AuNBPs, T-AuNBPs and preserved S-AuNBPs. (a) EM field intensity of S-AuNBP and T-AuNBP at 780 nm. SERS spectra of *p*-ATP adsorbed on (b) S-AuNBPs and (c) T-AuNBPs upon exposure to varying concentrations of *p*-ATP. SERS spectra of *p*-ATP collected from the T-AuNBP, S-AuNBP and preserved S-AuNBP papers after exposure to (d) 100 μ M and (e) 10 nM *p*-ATP solution, respectively. (f) SERS intensity of 1141 cm^{-1} Raman band of *p*-ATP collected from T-AuNBP, S-AuNBP and preserved S-AuNBP papers corresponding to varying concentrations of *p*-ATP. Error bars represent standard deviations from three locations of SERS substrates.

Figure 5.

Refractive index sensitivity of S-AuNBPs, T-AuNBPs and preserved S-AuNBPs. Extinction spectra of (a) S-AuNBPs and (b) T-AuNBPs measured in the medium with changing refractive indices, from air to varying concentrations of sucrose aqueous solutions (0-42 w/v%). (c) Corresponding LLSPR wavelength shift and fitted RIS curve for S-AuNBPs, T-AuNBPs, and Preserved S-AuNBPs. Extinction spectra of (d) S-AuNBPs and (e) T-AuNBPs following the conjugation with PA, IgG, and anti-IgG, respectively, and (f) corresponding comparison of LLSPR wavelength shifts of S-AuNBPs and T-AuNBPs after each conjugation step. Error bars represent standard deviations from three independent samples.

Figure 6.

ZIF-8 coating of biofunctionalized S-AuNBPs. (a) Schematic illustration of S-AuNBP-IgG bioconjugation, ZIF-8 coating, ZIF-8 removal and target (anti-IgG) binding. (b) Time evolution of the extinction spectra showing the growth of ZIF-8 coating around AuNBP-IgG and (c) corresponding LLSPR wavelength shift. (d) TEM image of AuNBP-PA-IgG after 5 minutes of ZIF-8 coating. (Magnification: 100,000X)

Figure 7.

Simultaneous preservation of S-AuNBPs and biomolecule with ZIF-8 exoskeleton. (a) Extinction spectra of S-AuNBP following each step in (Figure 6a), and (b) corresponding LSPR wavelength shift. (c) Extinction spectra of S-AuNBP, after bioconjugation, storage at 60°C for 48 hours, and anti-IgG binding. (d) Biorecognition retention comparison of S-AuNBP-PA-IgG with and without ZIF-8 protection. Error bars represent standard deviations from three independent samples.