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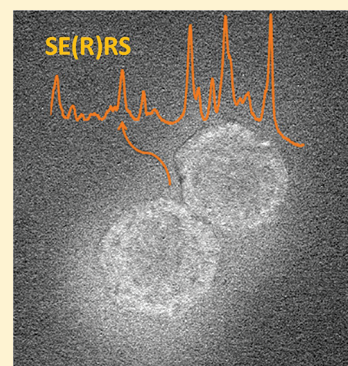
# Surface-Enhanced Raman Scattering Investigation of Hollow Gold Nanospheres

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## S Supporting Information

**ABSTRACT:** Hollow gold nanospheres (HGNs) provide a tunable surface plasmon resonance from 550 to 820 nm by controlling their inner diameter and wall thickness. Although they have been used for biological imaging based on their optical properties in the near-infrared region, their surface-enhanced Raman scattering (SERS) performance has not been thoroughly studied. Herein, HGNs with different surface plasmon resonances were synthesized and functionalized with different Raman reporters. HGNs coupled with Raman reporters, on and off resonant with the laser excitation wavelength, were systematically interrogated in isolated and partially aggregated situations. HGNs with thicker shells generated higher SERS responses than thinner shells no matter whether they were isolated, or partially aggregated, or whether their surface plasmon resonances were resonant with the excitation wavelength or not. This study gives insight into the basis of the SERS properties for these kinds of materials.



## INTRODUCTION

Surface enhanced Raman scattering (SERS) is an ultrasensitive vibrational spectroscopic technique that can be used for the detection of molecules on, or in close proximity to, the surface of metal nanostructures. SERS can provide a noninvasive molecular detection that can be tuned to the near-infrared (NIR) region, which is of significance since this region provides a clear window for both therapeutic and imaging applications in tissue.<sup>1,2</sup> The SERS enhancement originates from chemical and electromagnetic (EM) contributions,<sup>3–5</sup> and when a dye resonant with the interrogating laser is used, a further electronic enhancement results in surface-enhanced resonance Raman scattering (SERRS). EM enhancement depends on the large local field enhancements that occur close to metallic surfaces when localized surface plasmon (LSP) resonances are excited, and this is the dominant enhancement mechanism in the case of nonresonant absorbates such as biological molecules.<sup>3–5</sup>

There is a great need toward the development of substrates with a surface plasmon resonance (SPR) in the NIR region for biological SERS imaging due to the better penetration depth and reduced autofluorescence. SERS substrates are generally based on noble metal nanoparticles and salt-induced aggregation of noble metal nanoparticles is widely used to construct solution based SERS-active substrates. Aggregation creates SERS “hot spots” which are highly localized EM fields between metal nanoparticles.<sup>6</sup> Molecules placed in these areas generate large Raman signals and after optimization, single molecule detection can be achieved.<sup>7,8</sup> However, the use of aggregation does not produce a stable solution, rather it causes the metal nanoparticles to flocculate.<sup>9</sup>

Hollow gold nanospheres (HGNs) consisting of a spherical gold shell filled with embedding medium were synthesized

using cobalt (Co) nanoparticles as sacrificial templates, and gold shells were grown via galvanic reaction with Au<sup>3+</sup> ions.<sup>10,11</sup> The surface plasmon resonance in the region of 550–820 nm was controlled by tuning the inner diameter and wall thickness.<sup>10,12</sup> Generally, controlled aggregates of HGNs have a lower SERS activity than that obtained from random aggregates of silver or gold spherical nanoparticles, however their SERS response tends to be more uniform than other nanoparticle substrates.<sup>13</sup> Because of their optical properties and small sizes (usually from 30 to 60 nm), HGNs have been used for pH sensing,<sup>14</sup> SERS imaging of cancer markers in single cells,<sup>15</sup> on-chip immunoassays,<sup>16</sup> and as a DNA biosensor.<sup>17</sup>

SERS from metallic nanospheres<sup>9,18</sup> and nanoshells<sup>19,20</sup> have been extensively investigated. As a recently developed material, HGNs have been widely used due to their favorable optical properties; however their SERS performance has not been thoroughly investigated.<sup>13</sup> To gain a better understanding of the SERS response of HGNs, samples with different surface plasmon resonances were functionalized with different Raman reporters which were either on or off resonance with the laser excitation wavelengths. This study gives an insight into the basis of the SERS properties for these kinds of materials.

## EXPERIMENTAL DETAILS

**Synthesis of HGNs.** The synthesis of HGNs was carried out in a standard Schlenk line under Ar.<sup>10</sup> In a typical synthesis, 100  $\mu$ L of 0.4 M cobalt chloride hexahydrate (Fisher Scientific,

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99.99%) and 500  $\mu\text{L}$  of 0.1 M trisodium citrate dihydrate (Sigma-Aldrich, >99%) were added to 100 mL of deionized water and degassed several times. One mL of 0.1 M sodium borohydride (Fisher Scientific, 99%) was injected into the solution. This solution was allowed to react for 20 min, (under constant argon flow) until hydrogen evolution ceased, indicating complete hydrolysis of the reductant. Next, 33 mL of different concentrations ( $5 \times 10^{-5}$  M for HGN1 and  $1.5 \times 10^{-5}$  M for HGN2) of chloroauric acid trihydrate (Fisher Scientific, ACS reagent grade) was then injected under rigorous stirring. This mixture was reacted for a further 10 min under vacuum before being exposed to air. Finally, 500  $\mu\text{L}$  of 0.1 M sodium citrate was added under vigorous stirring to stabilize the HGNS, and a color change (from brown to light green) was observed.

After synthesis, the solution was concentrated through centrifugation ( $3466 \times g$ ). The precipitate was redispersed into 10 mL (HGN1) or 5 mL (HGN2) of 0.6 mM sodium citrate solution.

**Characterization.** Before SERS measurements, the concentrations of the hollow gold solutions were adjusted to the same level with the aid of a Nanosight LM10 via the procedure described in the instrument technical notes. Briefly, the original concentrated solutions were diluted with filtered milli-Q water until 20 to 60 nanoparticles per frame were obtained. The imaging videos were recorded for 60 s and analyzed using the provided software (NTA 2.1). The required dilution factor was then applied to the rest of the samples.

Investigations into the SERS properties of HGNS were carried out by mixing 135  $\mu\text{L}$  of the concentrated hollow gold solution (for HGN1, it was first diluted by half before use) and 15  $\mu\text{L}$  of different Raman reporters:  $2 \times 10^{-7}$  M *trans*-1,2-bis(4-pyridyl)-ethylene (BPE, Sigma-Aldrich, 97%) in water,  $2 \times 10^{-7}$  M NIR-797 isothiocyanate (Sigma-Aldrich,  $\geq 70\%$ ) in water, and  $2 \times 10^{-7}$  M Malachite green isothiocyanate (Invitrogen Life Science, UK) in water. This was followed by 150  $\mu\text{L}$  of water or 30 mM KCl; the samples were left to stabilize overnight before SERS measurements.

Two excitation wavelengths, 632.8 and 785 nm, were used during the SERS study. 632.8 nm solution SERS spectra were recorded using a Renishaw Ramascope system 2000 with a 632.8 nm line of a helium–neon laser as the excitation source. An Olympus  $20 \times$  /NA0.4 long-working distance objective was used for excitation and signal collection in a  $180^\circ$  backscattering geometry from a microcuvette. The unfocused power output was measured to be  $\sim 4.8$  mW at the sample. Dielectric edge filters were used to reject the Rayleigh scattered light. Spectra were accumulated for 10 s, and 5 replicates were carried out at each sample point; the signals were normalized to a cyclohexane standard.

785 nm solution SERS spectra were recorded using a 785 nm diode laser fiber optically coupled probe system attached to a Renishaw inVia microscope system, using an f18 focusing/collection lens. The power at the sample was measured to be  $\sim 90$  mW, and a 1200 groove diffraction grating was used. Spectra were accumulated for 10 s, and five replicates were carried out at each sample point; the signals were normalized to a cyclohexane standard.

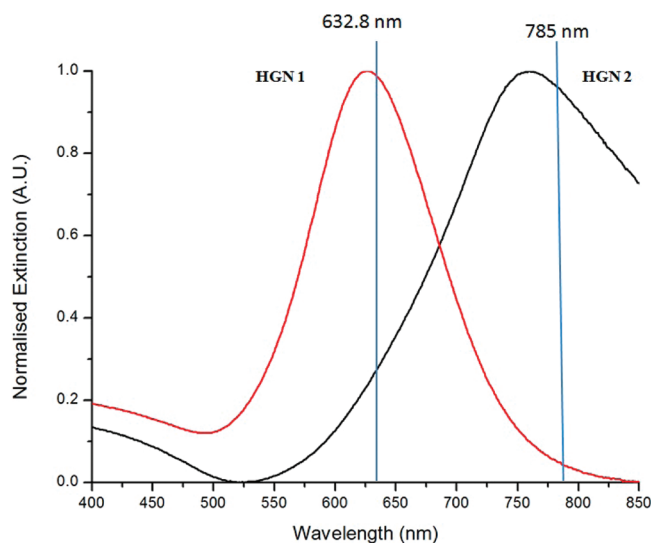
Samples for SEM analysis were prepared on polyelectrolyte functionalized silicon wafers as reported previously.<sup>21,22</sup> Briefly, wafers were cleaned using water and ethanol then dried in a  $\text{N}_2$  flow. They were then placed in an oxygen plasma cleaner for 60 s before being coated with poly(diallyldimethylammonium

chloride) (Sigma-Aldrich) (PDDA). Thirty  $\mu\text{L}$  of PDDA was dissolved in 1 mL of 1 mM NaCl and then dropped onto the clean wafer for 30 min under a water-saturated atmosphere before being washed off and dried in a  $\text{N}_2$  flow. 100  $\mu\text{L}$  of each HGN sample was put onto the PDDA-functionalized silicon wafer for 15 min under a water-saturated atmosphere. The sample was then washed off and dried in a  $\text{N}_2$  flow.

SEM was carried out on a Sirion 200 Schottky field-emission electron microscope operating at an accelerating voltage of 5 kV. The samples did not require additional metallic coating before imaging, and the particle size was analyzed using image J.

## RESULTS AND DISCUSSION

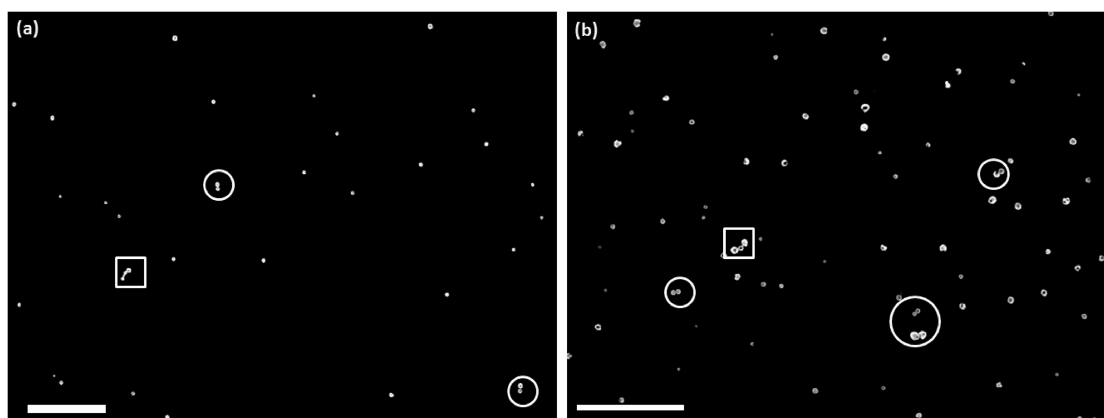
**Characterization of HGNS.** Two different sizes of HGNS, HGN1 and HGN2, with SPRs overlapping standard laser excitation wavelengths were synthesized. Their normalized extinction spectra are shown in Figure 1. HGN1 is resonant



**Figure 1.** Normalized extinction spectra of two types of HGNS. The laser excitations used in the SERS experiments are marked.

with 632.8 nm laser excitation and has an average size of  $54 \pm 6$  nm with a shell thickness of  $8.3 \pm 0.6$  nm, while HGN2 is resonant with 785 nm laser excitation and has an average size of  $65 \pm 9$  nm with a shell thickness of  $6.5 \pm 1.3$  nm.<sup>10,12</sup> In addition to the SPR of the nanoparticles, SERS is dependent on the number of nanoparticles present within the laser volume and the enhancement factor of each particle or cluster.<sup>18</sup> Therefore, to compare the SERS properties of different kinds of nanoparticle solutions, it is important to normalize the particle concentration. HGN1 was first diluted by half then further diluted by 1000x while HGN2 was diluted by 1000x directly before imaging was carried out using a NanosightLM10. The final concentrations of diluted solutions were found to be  $3.33 \times 10^8$  particles/mL for HGN1 and  $3.46 \times 10^8$  particles/mL for HGN2 under the same imaging conditions. Thus HGN2 had a very slightly higher particle concentration than HGN1 (diluted by half), but the difference in practical terms was deemed to be negligible.

**Aggregation Profiles of HGNS.** It has been stated that the majority of the SERS signal in an aggregated sample originates from a very small number of molecules on the surface of the nanoparticles.<sup>23</sup> Aggregation of nanoparticles results in the coupling of plasmons between particles leading to the



**Figure 2.** SEM images of partial aggregates of HGN1 (a) and HGN2 (b). The scale bar in each image is 1  $\mu\text{m}$ ; for clarity dimers are circled, and trimers are boxed.

**Table 1.** SEM Cluster Analysis, Values Are Percentages of Nanoparticles Involved in Each Cluster Type

	monomers	dimers	trimers	tetramers	small aggregates (5–10)	total colloid particles
isolated HGN1	96.3	2.3	1.4			218
partially aggregated HGN1	75.0	14.1	5.4	2.4	3.1	540
isolated HGN2	95.5	2.0	1.0	1.0	0.5	201
partially aggregated HGN2	78.1	15.8	4.5	1.0	0.6	494

formation of “hot spots” where the electromagnetic field is significantly enhanced.<sup>3</sup> Aggregation is achieved by the addition of an electrolyte, normally a simple inorganic salt, which screens the Columbic repulsion energy between the nanoparticles. The van der Waals attraction then dominates and coagulation of the colloid occurs.<sup>24</sup> Partial aggregation can create effective “hot spots” consisting of dimers and trimers.<sup>25</sup> Importantly, the formed solution does not form large clusters, which would sediment, and therefore it remains stable for a period of time, which is preferred for further analysis. A very low concentration of analyte (10 nM final concentration), which is insufficient to significantly affect the Columbic repulsion was used to avoid any aggregation caused by the addition of reporter molecules ensuring all aggregation was only induced by the salt.<sup>26,27</sup> The partial aggregation extinction spectra of HGN1 and HGN2 are shown in Figure S1 and S2 of the Supporting Information. For HGN2, a slight change was observed after the addition of analyte, but there was a negligible change for HGN1. The aggregation profiles of HGNS are quite different from that of normal gold and silver nanoparticles. A blue shift instead of a red shift was observed upon aggregation;<sup>28</sup> HGN2 showed a much larger shift compared to HGN1. The SPR of hollow gold is controlled by the thickness of the shell;<sup>12</sup> thus, from the extinction spectra it can be concluded that HGN2 has a thinner wall compared to HGN1 which was also observed in the TEM images. Upon aggregation of thin-shell HGNS, a pronounced, newly formed longitudinal SPR that was blue-shifted with respect to the transverse SPR of isolated HGNS was observed.<sup>29</sup> Importantly, this trend was analyte independent; therefore only nanospheres functionalized with malachite green are shown as an example.

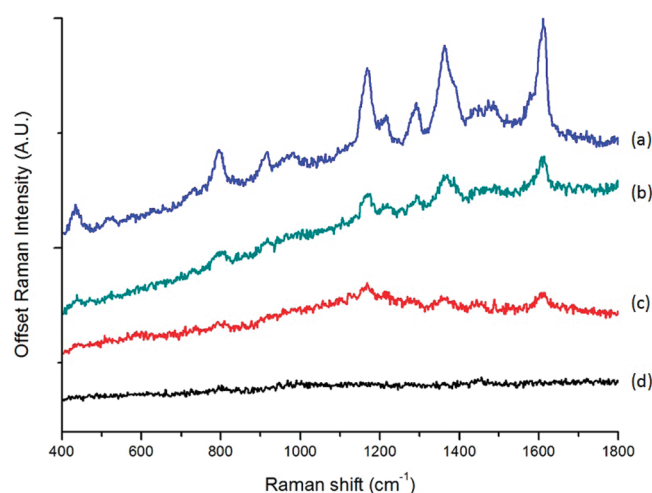
The aggregation states of HGNS prefucionalized with Raman reporters were investigated by SEM. HGNS were deposited on PDDA-functionalized silicon wafers, which were positively charged and could therefore capture the negatively charged nanoparticles. Deposition was carried out under a water-saturated atmosphere over 15 min to avoid the formation

of large surface aggregates due to the drying of nanoparticle solutions. Figure 2 shows typical SEM images of partially aggregated HGN1 and HGN2 samples. For clarity, dimers and trimers are marked with different shapes. Through careful examination of the original SEM images it could be seen that the surface of HGN1 particles were complete while there were several obvious cavities on the surface of the HGN2 particles (Figure S3 of Supporting Information). The number and size of the aggregates formed were counted, and the percentages of particles involved in each sample are reported in Table 1. The approach we have undertaken was found to ensure that the observed aggregates deposited onto the surface were representative of those in solution due to a controlled deposition time and by focusing on the use of comparative studies rather than absolute assignment of aggregate morphology percentages.

The isolated HGNS, without salt addition, were found to contain small numbers of dimers and trimers, but the vast majority of particles existed as monomers. The addition of a salt concentration of 30 mM KCl reduced the percentage of monomers and increased the percentages of dimers, trimers, and tetramers. As the number of aggregates formed is sensitive to the concentration of nanoparticles and equilibration time, differences between HGN1 and HGN2 should be small since their concentrations were very similar before salt addition. In addition, as low concentrations of Raman reporters were used, the aggregate status was found to be analyte independent.

**SERS Performance of HGNS.** Malachite green is resonant with 632.8 nm excitation therefore an extra enhancement is expected from the dye. The SPRs of isolated, and partially aggregated HGN1 shows that this substrate is also resonant with the excitation wavelength (Figure S1 of Supporting Information). Although the isolated HGN2 has a SPR of 760 nm, a large blue shift (around 100 nm) caused by the addition of 30 mM KCl brought it close to the resonance region of 632.8 nm excitation (Figure S2 of Supporting Information). Figure 3 shows the offset SERS spectra of malachite green from the





**Figure 3.** SERS spectra of malachite green using 632.8 nm excitation wavelength, spectra have been offset for clarity. (a) Partially aggregated HGN1; (b) isolated HGN1; (c) partially aggregated HGN2; (d) isolated HGN2.

different substrates using 632.8 nm excitation. Unlike isolated HGN1 (Figure 3b), nonaggregated HGN2 (Figure 3d) gave negligible SERS presumably due to the small overlap between the SPR and the excitation wavelength. Both partially aggregated HGN1 and HGN2 samples show increased signal compared to when they were nonaggregated. As previously described, nanoparticle aggregates form “hot spots” where the electromagnetic field is significantly increased. Importantly, when HGN2 was partially aggregated, its SPR was close to the 632.8 nm laser excitation. (Figure S2 of Supporting Information) However, even when partially aggregated, the SERS signal intensity of HGN2 was of a similar level to isolated HGN1 under the same experimental conditions.

When the nonresonant reporter molecule BPE was added to HGN and 632.8 nm excitation was used, the signal was significantly weaker but still distinguishable above the background. Partially aggregated HGN2 generated the same signal intensity as the isolated HGN1 sample. The similar trends observed regardless of whether resonant or nonresonant molecules are analyzed demonstrate that the effect is molecule independent.

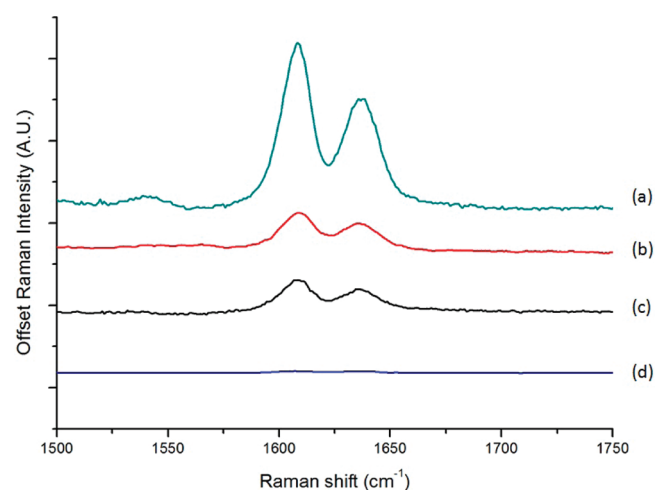
When the laser excitation was changed to 785 nm, isolated and partially aggregated HGN1 were no longer resonant (Figure S1 of Supporting Information); however the isolated HGN2 were in resonance (Figure S2 of Supporting Information). Surprisingly, isolated HGN2 functionalized with BPE still gave negligible signals (Figure 5d). As shown in Figure 5, the partially aggregated HGN1 (Figure 5a) still gave the highest SERS intensity despite having a SPR maximum away from the laser excitation wavelength. Importantly, the particle concentration of isolated HGN1 was slightly lower than that for HGN2 and is off resonance with respect to the laser excitation.

To rule out the influence of the reporter molecule, NIR-797 dye which is resonant with 785 nm excitation was used and a similar trend was observed (Figure S4 of Supporting Information). In addition, different batches of HGN1 and HGN2 were used to repeat the experiments under the same conditions. Although slight SERS intensity variations were observed, the same trends were obtained.

**Discussion of SERS Properties of HGNS.** From the SERS results, HGN1 was observed to generate a higher SERS



**Figure 4.** SERS spectra of BPE at 632.8 nm excitation. (a) Partially aggregated HGN1; (b) isolated HGN1; (c) partially aggregated HGN2; (d) isolated HGN2.



**Figure 5.** SERS spectra of BPE at 785 nm excitation. (a) Partially aggregated HGN1; (b) isolated HGN1; (c) partially aggregated HGN2; (d) isolated HGN2.

performance than HGN2 irrespective of whether it was isolated or partially aggregated or its SPR was resonant with the laser excitation or not. Recently, Chandra et al. simulated the electric field spatial profiles of HGNS with fixed outer diameters but different wall thicknesses.<sup>29</sup> For isolated HGNS, when the shell became thinner, the outer electric field decreased when compared to thicker shell particles.<sup>29</sup> The same theoretical results were also obtained for hollow nanoframes.<sup>30</sup> Herein, the reporter molecules were attached to the outer surface thus it is reasonable to expect that HGN1, with its thicker shell, generates higher SERS signals than HGN2. When isolated HGNS became partial aggregates, the particles were in contact as seen by the blue shifts in the extinction spectra.<sup>28,29</sup> In electric field calculations of touching nanoshells, a significant electric field was observed along the cavity walls when HGNS with thinner shells were in contact with each other. In contrast, HGNS with thicker shells exhibited the majority of the electric field intensity at the conical region at the particle interface.<sup>29</sup> Therefore, an increase signal was observed for every SERS measurement carried out in partially aggregated samples compared to their individual samples. The signal differences

obtained between partially aggregated HGN1 and HGN2 is assumed to be because of the intrinsically weak electric field distribution of HGN2. In addition, surface pin-holes formed during the synthesis are considered to generate an extra enhancement in the surface electric field.<sup>12,16</sup> In fact, from SEM images, obvious cavities were observed on the surface of HGN2 (Figure S3 of Supporting Information). Although surface cavities can provide a red-shifted surface plasmon resonance,<sup>31</sup> these holes are too big to play a role in enhancing the surface electric field. In addition, HGN2 is larger than HGN1 and has a larger surface area; therefore, with the same analyte concentration, HGN2 should load at least an equal amount of analyte on the surface yet it generates lower signals. Hence, although HGN2 with its thinner shell generates a red-shifted SPR, it is not a good choice for a SERS substrate based on the experimental results which are also backed up with the previously published electric field distribution simulations.

## CONCLUSIONS

HGNs with different surface plasmon resonances were synthesized and functionalized with different Raman reporters. HGNs and Raman reporters on and off resonance with standard laser excitations were systematically interrogated in isolated and partially aggregated situations, respectively. HGN1, which had a thicker shell, always gave a higher SERS performance than HGN2 independent of whether it was resonant with the laser excitation or not. For isolated HGNs, when the shell thickness becomes thinner, the outer electric field decreased. When isolated HGNs became partially aggregated, a significant electric field was observed at the particle interface. The signal differences between HGN1 and HGN2 in the partially aggregated situation is due to the intrinsically weak electric field distribution of HGN2. This suggests that it may be worth trying functionalization of the inner wall of thin shelled HGN based on the spatial electric field distribution maps.

## ASSOCIATED CONTENT

### Supporting Information

The extinction spectra of partial aggregates of HGN1 and HGN2 and SERS spectra of NIR-797 from different substrates at 785 nm excitation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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