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Molecularly Mediated Processing and Assembly of Nanoparticles: Exploring the Interparticle Interactions and Structures

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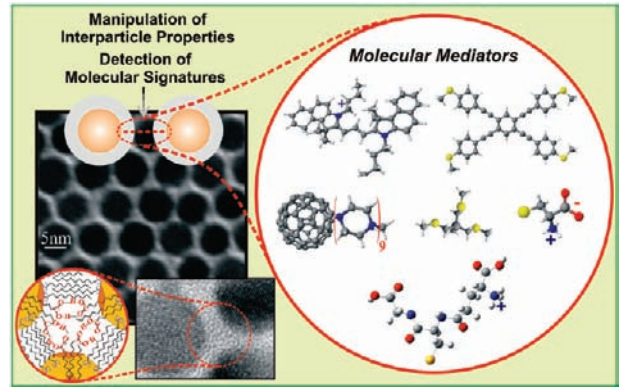
CONSPECTUS

The harnessing of the nanoscale properties of nanoparticles in most technological applications requires the abilities of controlled processing and assembly, which has been an important challenge because of the difficulty in manipulating interparticle properties. Molecularly mediated processing and assembly of nanoparticles have emerged as an important strategy for addressing this challenge. The capability of this strategy in manipulating size, shape, composition, and interparticle properties has significant implications for designing sensing, biosensing, nanoprobing, and many other functional nanostructures. This Account highlights some of the important findings in investigating both interparticle and collective properties as a forum for discussing new opportunities in exploiting nanoparticle-based designs and applications.



The concept of mediator−template assembly of nanoparticles explores the combination of the forces from a mediator and a templating molecule for designing and controlling the interparticle interactions. The manipulation of the interparticle interaction properties and the detection of the molecular signatures are two of the key elements in this concept. A series of well-defined molecular mediators ranging from inorganic, organic, supramolecular, to biological molecules have been explored to ascertain how these two elements can be achieved in nanoparticle assemblies. The emphasis is the fundamental understanding of interparticle molecular interactions, such as covalent, electrostatic, hydrogen bonding, multidentate coordination, $\pi-\pi$ interactions, etc. Each of these molecular interactions has been examined using specific molecules, such as multifunctional ligands, tunable sizes, shapes, or charges, well-defined molecular rigidity and chirality, or spectroscopic signatures, such as fluorescence and Raman scattering. Examples included thiols, thioethers, carboxylic acids, fullerenes, dyes, homocysteines, cysteines, glutathiones, proteins, and DNAs as molecular mediators for the assembly of gold, alloy, and magnetic nanoparticles.

The understanding of these systems provided insights into how the unique electrical, optical, magnetic, and spectroscopic properties of the nanoparticle assemblies can be exploited for potential applications. This Account also highlights a few examples in chemical sensing and bioprobing to illustrate the importance of interparticle interactions and structures in exploiting these properties. One example involves thin-film assemblies of metal nanoparticles as biomimetic ion channels or chemiresistor sensing arrays by exploiting the nanostructured ligand framework interactions. Other examples explore the surface-enhanced Raman scattering signature as nanoprobes for the detection of protein binding or the enzyme-based cutting of interparticle DNAs. The detailed understanding of the design and control parameters in these and other systems should have a profound impact on the exploration of nanoparticles in a wide range of technological applications.

Introduction

An important challenge in harnessing the nanoscale properties of nanoparticles in technological applications involves controlled processing and assembly. Part of the challenge is attributed to the difficulty in manipulating the size, shape, and

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interparticle properties. One major approach to this challenge deals with acquiring the nanoscale properties from isolated nanoparticles, e.g., single nanoparticle quantum effect.[1,2] This ability requires atomic precision in nanoparticle fabrication. Another approach explores the nanoscale properties from an ensemble of nanoparticles, e.g., thin-film or DNA-linked assemblies.[2−4] This ability requires controlled assembly of nanoparticles. In either case, the ability to engineer the nanoscale properties is essential and has been the subject of extensive reviews in recent years.[1−5] In this Account, we highlight some of the insights gained from recent studies of molecularly mediated processing and assembly of nanoparticles in terms of size, shape, composition, and interparticle properties. In addition to technological applications in chemical sensors, biosensors, and diagnostic probes, the strategy of molecularly mediated processing and assembly allows for fine tuning of the interparticle properties at the molecular level. This level of control also provides an advanced understanding of the phenomena of aggregation, which has long been a subject of research on small-sized particles. Much of the understanding on the interparticle forces for aggregation has been based on van der Waals, magnetic, electrostatic, solvation, depletion, capillary, friction, and lubrication forces.[6] For example, the kinetic stability is often approached by considering the energy barrier of two approaching particles based on the classical Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory, where the basic assumption is the superposition of repulsive electric double layers and attractive van der Waals potentials. Relatively less attention has been given to understanding how interparticle molecular structures and interactions are operative in aggregation, including hydrogen bonding, covalent or electrostatic binding, ligand−metal coordination, and $\pi-\pi$ interactions. This understanding is important for the assembly of nanoparticles toward functional materials with molecularly defined interparticle molecular signatures for chemical and biological sensing or probing applications.

The fact that nanoparticles and assemblies exhibit unique electrical, optical, magnetic, and catalytic properties is not only because of the dramatic increase in the surface area/volume ratio as the particle size is reduced but also because of the emergence of collective and nanoscale properties as a result of the interparticle arrangement or assembly. It is the exploration of such nanostructures that has captured the growing interests of research at the interfaces of chemistry, physics, biology, and materials science. While many nanoparticles exhibit unique electronic properties different from their bulk counterparts, the incorporation of macromolecules such as fullerenes, into metal or semiconductor nanoparticles produces interesting photoinduced charge transfer and separation.[7,8] The electrical properties of thin-film assemblies of metal nanoparticles mediated by bifunctional mediators have been exploited for chemiresistor sensing,[9−14] where the sorption of volatile organic compounds (VOCs) leads to a change in electron hopping or tunneling properties depending upon particle size, interparticle distance, and medium properties. Other functional materials exploit the optical properties of nanoparticles and assemblies, such as light scattering and surface plasmon (SP) resonance, which have been a subject of numerous reviews.[2−5] In addition, understanding how the optical properties correlate with the interparticle molecular interactions is increasingly important for nanoparticle assemblies in thin films[12,15,16] or in solutions mediated by amino acids,[17−19] dyes,[20] and fullerenes,[21,22] because of the ability to detect or manipulate their interparticle structural properties.[23] For example, the understanding of how the surface-enhanced Raman scattering (SERS) effect of molecules on gold and silver nanoparticles is related to interparticle "hot spots" has captured growing interests in both experimental and theoretical investigations.[24−26] Applications of the research include labeling of protein-functionalized gold and magnetic nanoparticles for detecting specific antibody/antigen-binding events[27,28] and exploiting gold-coated magnetic core@shell nanoparticles and assemblies[29−31] for spectroscopic bioassay coupled with magnetic bioseparation.

A key to the exploitation of these unique nanoscale properties is the ability to control the interparticle structures and interactions in the nanoscale processing and assembly. Many strategies have been developed for the synthesis of different types of nanoscale materials,[32,33] including metallic, semiconductor, and oxide materials in the form of nanoparticles, nanowires, nanotubes, nanorods, etc. The exploitation of the melting-point decrease of nanoparticles for thermal processing of nanoparticles in terms of size, shape, and composition is an important strategy that combines surface-melting and surface-tension effects as part of the driving force for a controlled interparticle coalescence. This strategy has been demonstrated for temperature-controlled processing of gold, copper, alloy, and magnetic core−shell nanoparticles.[27,34,35] There are also various approaches to the assembly of nanoparticles for exploring the collective interparticle properties,[1,3,4] such as layer-by-layer stepwise assembly,[2,4] polymer- or dendrimer-mediated assembly,[36] and DNA-mediated assemblies.[37] The approach based on the concept of mediator−template assembly[38−41] explores a combination of a mediation force from the interparticle specific binding chem-

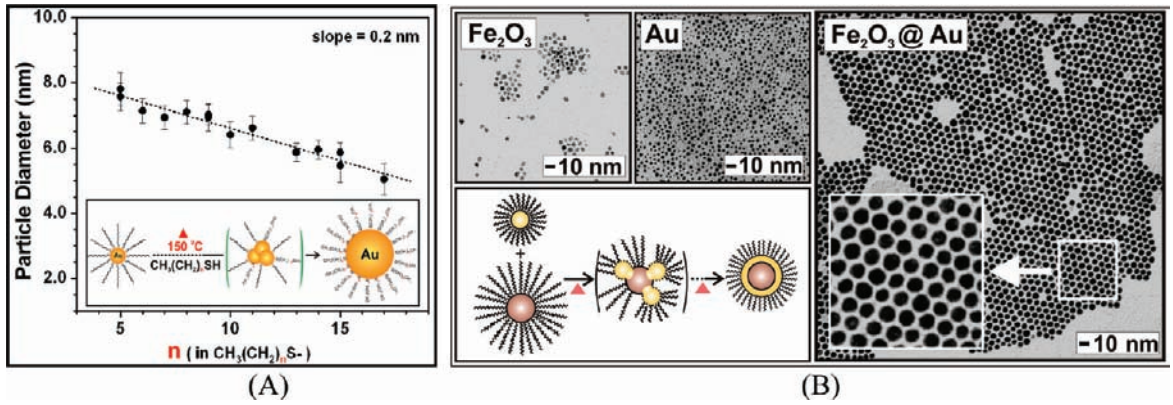

FIGURE 1. Thermally activated processing of metal and metal oxide nanoparticles. (A) Dependence of the particle size upon capping alkyl chain length with 2 nm Au precursor particles. (B) Formation of Fe_2O_3@Au nanoparticles with Au and Fe_2O_3 precursor nanoparticles.

istry (e.g., gold−thioether coordination, hydrogen bonding, etc.) and a templating force from the molecular interactions via capping molecules (e.g., van der Waals interaction) for the assembly of nanoparticles with controlled overall shape and size. This combination allows for effective manipulation of the interparticle structures for gaining insights into the aggregation phenomena of small particles, which are traditionally based on considerations of van der Waals and electrostatic interactions.[6] Discussions of the overall morphologies and spacing in nanoparticle assemblies[11,16,18,19,21,22,39,41] have often been the focus in other recent reviews on similar topic areas. We chose to focus on highlighting some of the insights in understanding the interparticle molecular interactions for the assembly of nanoparticles by different molecular mediators because it provides a fresh look from the perspective of exploring the interparticle molecular structural properties for the design of functional nanomaterials. While there are studies on 2D/3D ordering[11,16,39] and size or spacing correlation of electrical and optical properties for nanoparticle assemblies,[12,15,16] examples involving spectroscopic signatures were selected to address how the interparticle properties can be detected, and those involving chemical sensing based on the interparticle architectures were selected to address how the collective properties can be exploited.

Interparticle Structures and Interactions in Molecularly Mediated Assembly of Nanoparticles

This section starts by briefly describing the thermally activated processing of nanoparticle sizes and core−shell structures and continues with selected examples of the nanoparticle assemblies mediated by specific interparticle molecular interactions. The inclusion of a discussion on particle size and composition engineering stems mainly from the consideration of their important roles in determining the interparticle structures and exploring the interparticle-based sensing properties.[10−12] Examples are selected to illustrate some of the intriguing interactions or new properties, including interparticle chiral recognition, template−mediator effect, and molecular stacking as a result of molecular adsorption on the particles.

Thermally Activated Processing of Particle Size and Core−Shell Structure. While the dramatic decrease in melting point for many metal or alloy nanoparticles with size is a well-known phenomenon,[34] the exploitation of this phenomenon for processing the size and morphology of nanoparticles in solutions [e.g., Au, Cu, AuAg, AuPt, and Fe_2O_3 (or Fe_3O_4)@Au][27,29,34,35] under mild elevation of temperatures (100−200 °C) is relatively new. In contrast to Osterwald ripping known for small-particle systems, the thermally activated processing of a solution of presynthesized nanoparticles involves coupling of the molecular capping and re-encapsulation to the interparticle coalescence. One example is shown in Figure 1A for the size growth of the presynthesized gold nanoparticles (2 nm) as a function of chain length of the capping alkanethiols.[35] The increase in chain length of the capping alkanethiolates leads to a gain in stabilization energy because of interchain cohesive interactions, consistent with the known linear correlation of cohesive energy of the alkyl chains (~1 kcal/mol CH_2). This chain-length-dependent stabilization energy contributes to a balance of alkanethiolate desorption, core coalescence, and re-encapsulation in the particle-size evolution.[35] A longer chain length has a higher cohesive energy and leads to a size growth smaller than those with a shorter chain encapsulation.

Another example includes the fabrication of core@shell-structured Fe_2O_3 (or Fe_3O_4)@Au nanoparticles by a thermally activated hetero-interparticle coalescence route (Figure 1B).[27,29] In this case, the surface-melting temperature of the precursor 2 nm sized gold nanoparticles is much lower than that for the 5 nm sized iron oxide nanoparticles. The interpar-

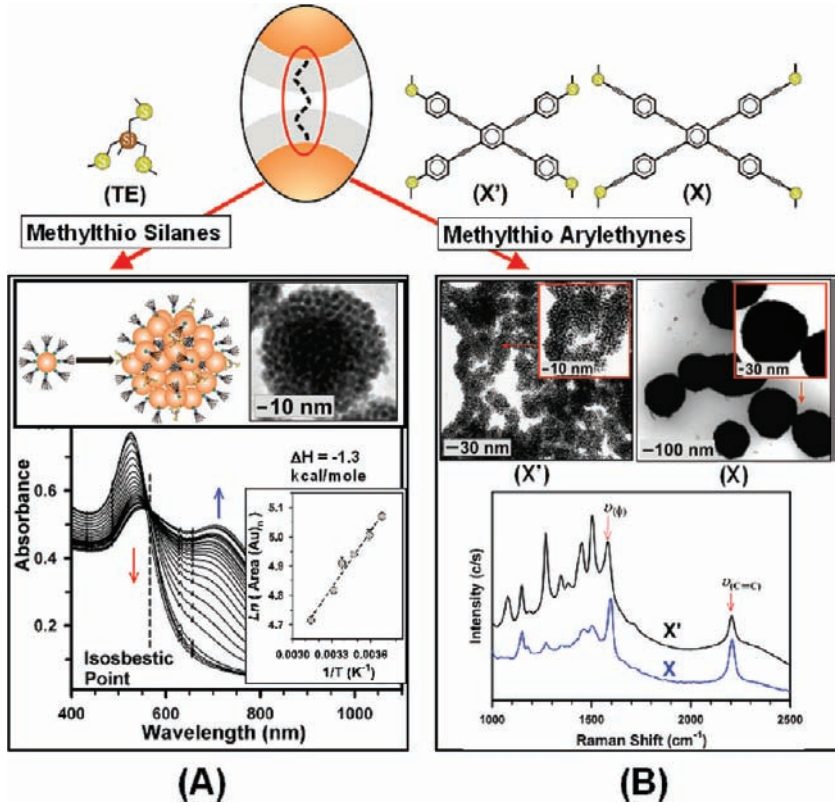

FIGURE 2. Mediator−template assemblies of TOA-capped gold nanoparticles mediated by (A) TE and (B) MTA in toluene solutions. (A) TEM and SP band. (B) TEM and SERS spectra.

ticle heterocoalescence of gold-coated iron oxides leads to the formation of core−shell nanostructures. In comparison to Fe_3O_4, the decrease in magnetization and the blocking temperature for Fe_3O_4@Au reflects the decreased coupling of the magnetic moments as a result of the increased interparticle spacing for the magnetic cores by a combination of the gold and the organic capping shells.[29] While the magnetization is reduced because of shell thickness effects, the fact that such core−shell nanoparticles are capable of functioning in magnetic bioseparation renders the thermally activated interparticle processing pathway as a design strategy for magnetic core−shell nanostructures.

Interparticle Interaction Mediated by Multidentate Coordination. Multidentate coordination of molecules in between nanoparticles is an important type of interparticle interaction that leads to the assembly of clusters of nanoparticles in solutions. In contrast to the coordination of thioethers to gold via a lone pair of electrons on sulfur-forming thioether-capped gold nanoparticles,[42] multidentate thioethers (TE) have been exploited as mediators for the assembly of gold nanoparticles.[38−41] One example involves the use of small methylthio silanes [e.g., $Si(CH_2SCH_3)_n$, $n = 2-4$, e.g., tris-[(methylthio)methyl]silane ($n = 3$, a tridentate thioether)] to explore a mediator−template combination of the interparticle multidentate coordination via sulfur groups and the hydrophobic templating force of the capping tetraoctylammonium (TOA) on gold nanoparticles for their assembly into size-controllable spherical clusters of nanoparticles (Figure 2A) in solutions.[38−40] The discussion on the number of particles and spacing in the spherical clusters has been documented.[39] The kinetic and thermodynamic analyses revealed that the mediator−template assembly is an enthalpy-driven process with $\Delta H \sim -1.3$ kcal/mol, which is close to the magnitude of van der Waals interaction energy for alkyl chains.[40]

Similar to the multidentate methylthiosilanes, rigid and shaped, multidentate methylthio arylethynes (MTA) consisting of a central benzene ring with four thioether-functionalized ligands with subtle differences in the structure next to the methylthio group, e.g., with (X) or without (X′) a triple bond, have also been demonstrated for the assembly of gold nanoparticles (Figure 2B).[41] The evolution of the SP band and the morphology of the assembly largely resemble those for the small methylthiosilanes but exhibit subtle differences in the red shift of the long-wavelength SP band and the less-spherical shapes of the clusters. Other structurally similar molecules, such as thioacetyl-terminated phenylacetylene, were shown earlier for the assembly of metal nanoparticles into dimers, trimers, or tetramers.[43] In addition to fine tuning the interparti-

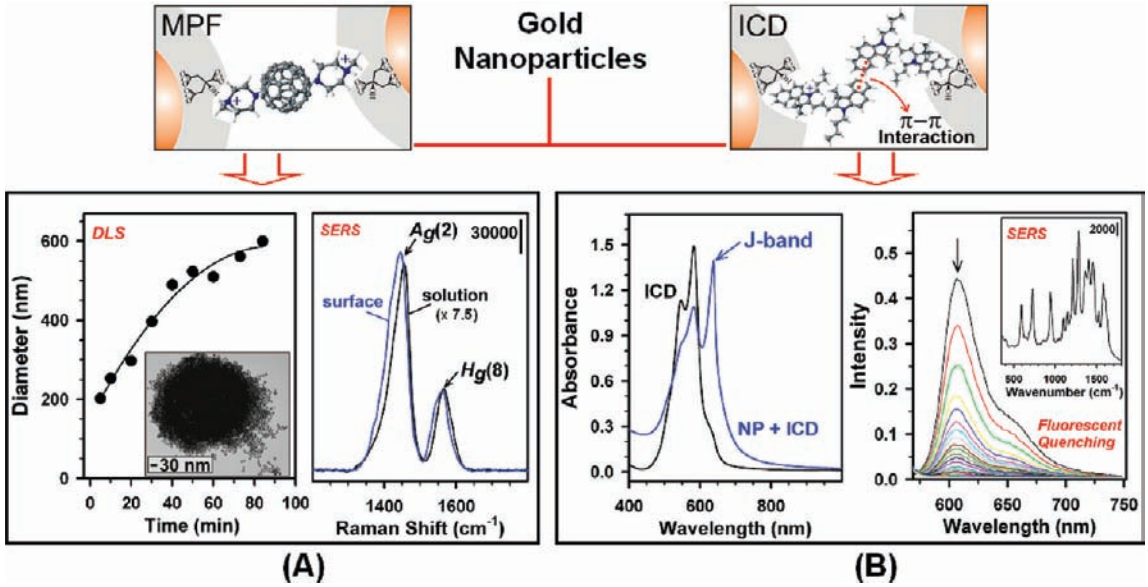

FIGURE 3. Assembly of citrate-capped Au nanoparticles mediated by (A) MPF and (B) ICD. (A) Growth of D_h (inset: TEM) and SERS spectra comparing the surface and solution samples for MPF−Au assembly and (B) UV−vis, fluorescence, and SERS spectra for ICD−Au assembly.

cle spacing and morphology and inducing their disassembly by a stronger ligand (e.g., alkanethiol),[41] the observation of SERS spectra characteristic of triple bond ($\nu_{(C\equiv C)}$) and benzene breathing ($\nu_{(\phi)}$) modes (Figure 2B) has implications to probing the interparticle "hot spot".

Fullerene- and Dye-Mediated Assemblies via Electrostatic and $\pi-\pi$ Interactions. In contrast to the interparticle multidentate coordination bonds with intimate interactions with the nanocrystals, interparticle electrostatic or $\pi-\pi$ interactions occur at charged functional groups or aromatic functionalities in the capping layer. Examples include assembly of nanoparticles mediated by multifunctional fullerene and fluorescent cyanine dyes via interparticle electrostatic interactions coupled with hydrophobic and $\pi-\pi$ interactions[20−22] or simply via van der Waals interactions.[44,45] An important driving force for studying the fullerene−nanoparticle assembly is to harvest the unique electron or energy-transfer properties as shown for photoactive antenna systems consisting of gold nanoparticle cores and the appended fullerene as the photoreceptive shell[7] and photon−current conversion by electrostatic assembly of functionalized C_{60} (e acceptor) and CdTe nanoparticles (e donor).[8] The interaction between the multifunctional C_{60} and molecularly capped nanoparticles[21,22] provides an interesting system for defining the interparticle properties by the macromolecular and multifunctional electrostatic interactions. The assembly of negatively charged Au nanoparticles in solutions by the positively charged piperazinyl groups on C_{60} derivatives, e.g., 1-(4-methyl)-piperazinyl fullerene (MPF) (nine positive charges per fullerene), is demonstrated by the increase of the hydrodynamic diameter (D_h) (Figure 3A). The detection of the Raman-active vibration modes [$A_g(2)$ and $H_g(8)$] of C_{60} is indicative of the SERS effect, substantiating the adsorption of MPF on the nanoparticle surface in the MPF−Au assembly. The slight red shift in the $A_g(2)$ and $H_g(8)$ peaks (~10 cm^{-1}) in comparison to those of the pristine C_{60} film is due to the interfacial interaction and charge transfer for C_{60} in the nanoparticle assembly.[46] These findings also have implications for the delineation between the interparticle interactions and the SERS effect for designing spectroscopic and optical probes.

The adsorption of dye molecules on nanoparticles is of interest in photochemical exploration and biodetection. As demonstrated for the recognition of DNA,[47] the formation of a helical double-stranded structure separates the fluorophore from the nanoparticle surface to restore the fluorescence. There is a need for detailed understanding of the interparticle interactions and reactivities for dye-mediated assemblies. In a recent study of the assembly of Au nanoparticles mediated by positively charged indolenine cyanine dyes (ICDs), the formation of interparticle J-aggregate bridges was identified in addition to the usual electrostatic and hydrophobic interactions (Figure 3B).[20] The one-dimensional arrangement in a J-aggregate is such that the transition moments of monomers are aligned parallel to the line joining their centers in an end−end fashion, in contrast to the parallel allignment being perpendicular to the line joining their centers in a face−face fashion in an H-aggregate. The spectroscopic evolution of the J-band, the surface plasmon resonance band, and the fluorescence quenching provide important information for assessing the SERS effect. While the formation of H-aggreagtes for

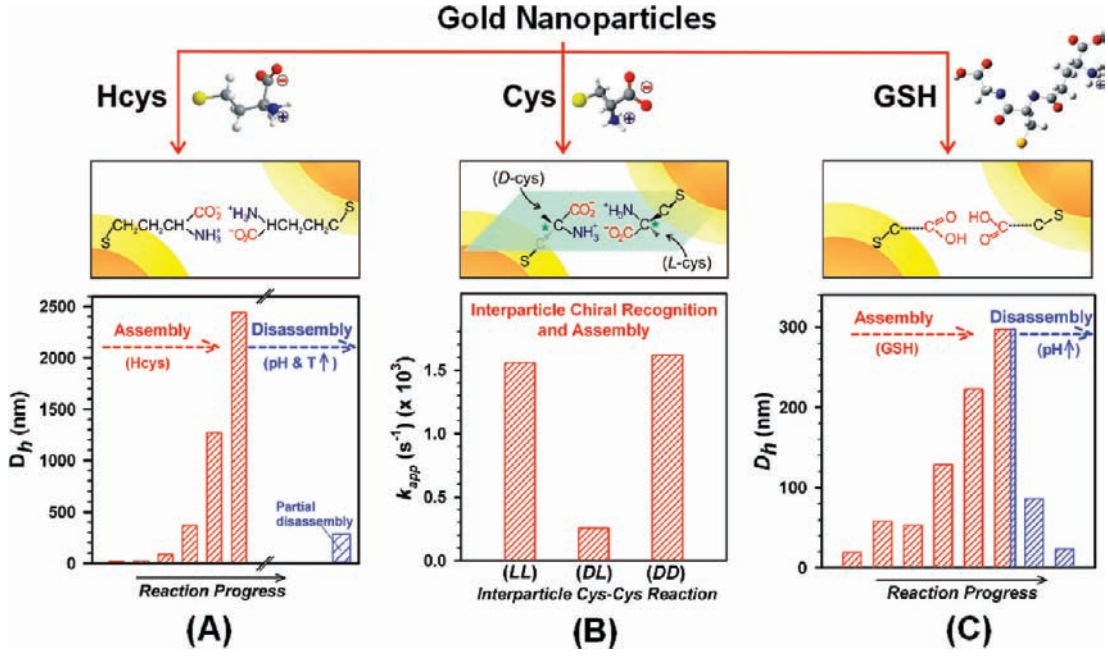

FIGURE 4. Assemblies of gold nanoparticles mediated by (A) Hcys, (B) Cys, and (C) GSH. (A) Zwitterionic interaction and the change of D_h for Hcys−Au assembly/disassembly. (B) Interparticle chiral recognition and the apparent rate constants for assembly of D- and L-Cys enantiomers. (C) Hydrogen-bonding interaction and the change of D_h for GSH−Au assembly/disassembly. The drawing of single-pair-mediating molecules is only for illustrative purposes.

Rhodamine 6G on gold nanoparticles as a result of intermolecular interactions[48] and J-aggregates for nanoparticles of synthetic clay or silica coated with cyanine dyes or polymers in water[49] is known, a deeper understanding of how such interactions are operative in the assembly of nanoparticles is needed. This was assessed recently[50] in a quantum mechanical modeling study by considering the transition-dipole coupling with a continuum of nanoparticle states to explain the enhancement of resonance Raman and fluorescence of molecules adsorbed on nanoparticles.

Assemblies Mediated by Thiol-Containing Amino Acids and Peptides. There is an increasing interest in understanding the detailed interparticle interactions with biomolecular relevance or specificity, including amino acids [e.g., homocysteine (Hcys) and cysteine (Cys)], peptides [e.g., glutathione (GSH)], proteins, and DNAs.[3] Hcys is a thiol-containing amino acid formed as an intermediate of the metabolism of methionine to cysteine. A level of both reduced and oxidized forms above the normal range in blood (5−15 μM) is used as an indication of cardiovascular disease and other medical disorders. The Hcys-mediated assembly of gold nanoparticles can be detected by monitoring the surface plasmon resonance absorption and dynamic light scattering (Figure 4A).[18] The strong interparticle zwitterion-type electrostatic interaction of the amino acids is supported by the slow disassembly of the nanoparticle assembly upon increasing pH at ambient temperature and its acceleration at elevated temperature. The understanding of such interparticle interactions is important for a better use of gold nanoparticles as a colorimetric or fluorimetric nanoprobe to the amino acids (e.g., homocysteine thiolactone[51]). This type of interparticle zwitterion-type electrostatic interaction is also found for Cys in a recent study that demonstrated the viability of nanoparticle-regulated chiral recognition of the cysteines in solution.[52] The pairwise zwitterion interaction of enantiomeric cysteines (D- and L-Cys) adsorbed on gold nanoparticles creates a chiral footprint for interparticle enantiomeric recognition, as demonstrated by the fact that the apparent kinetic rate constants for DD or LL cysteine-mediated assembly of nanoparticles are much higher than that for the enantiomeric mixture (DL) (Figure 4B). This finding is significant for understanding molecular chirality of basic amino acids and has potential applications in medicine for specific targeting because Cys is essential to the function of many proteins and enzymes. One recent example involves colorimetric detection of cysteine using DNA-functionalized Au nanoparticles in the presence of mercury ions.[53]

GSH, a tripeptide containing a cysteine, glutamic acid, and glycine moiety with a SH group, is found in the cytoplasm and acts as a reducing agent or antioxidant in the biochemical process. In contrast to Hcys and Cys, the interparticle interactions in the GSH-mediated assembly were found to involve prima-

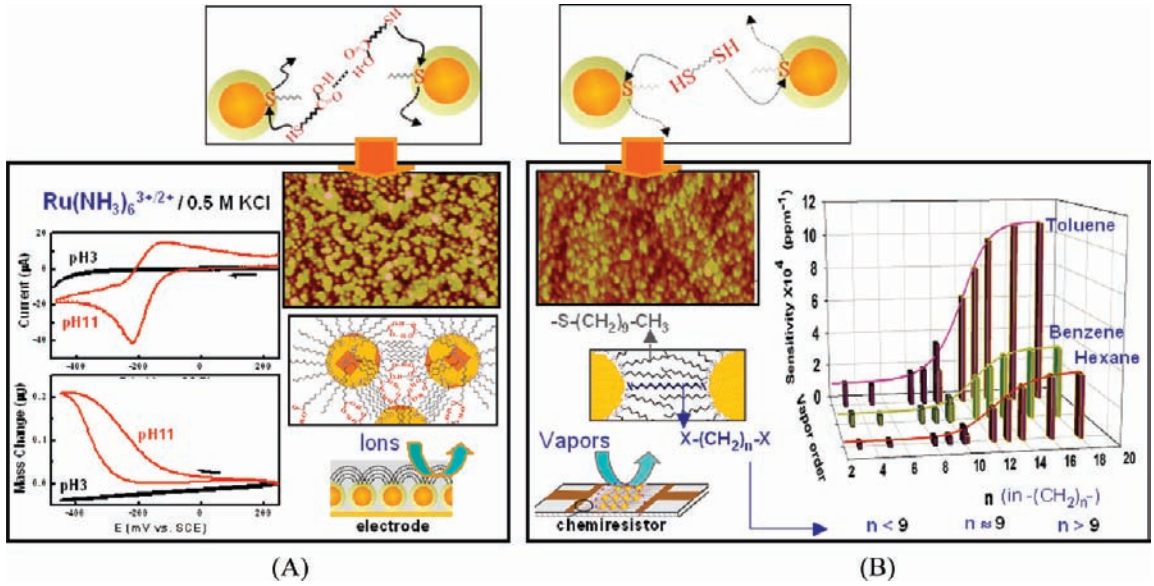

FIGURE 5. Thin-film assemblies of decanethiolate-capped gold nanoparticles mediated by (A) 11-mercaptoundecanoic acid and (B) alkyl dithiols or dicarboxylic acids of different chain lengths and their interfacial sensing properties. (A) Voltammetric and piezoelectric curves for a redox probe (50 mV/s). (B) Response sensitivities to VOCs for a chemiresistor array consisting of thin-film assemblies of nanoparticles with different interparticle spacing.

rily hydrogen bonding, with which the assembly and disassembly processes can be finely tuned by pH and monitored by the evolution of surface plasmon resonance bands and hydrodynamic sizes of the nanoparticle assemblies (Figure 4C).[19] The finding of the hydrogen-bonding character of the interparticle interaction of glutathiones on gold nanoparticles is significant for exploring potential applications. There are recent examples demonstrating GSH-responsive drug-delivery-release nanoparticle systems[54] that explore the surface-exchange reaction of GSH on gold nanoparticles with a mixed monolayer composed of [tetra(ethylene glycol)lyated] cationic ligands and thiolated Bodipy dye.

In addition to biologically relevant amino acids and tripeptides, another frontier in the exploration of the assembly of nanoparticles involves the detection of protein and DNA in various biological systems.[3,37] Recent studies of nanoparticle assembly based on DNA-complementary binding and disassembly based on restriction enzyme cutting[55,56] provide insights into the molecular intervention of the interparticle biomolecular interactions. The specific and selective binding activity between antibodies and antigens on nanoparticles has been exploited as a means of sandwich-type immunoassay via SERS readout and has the capability of multiplexed assay, which was recently expanded to the interparticle assembly between reporter-labeled Au nanoparticles and magnetic core@Au nanoparticles for achieving both magnetic bioseparation and SERS-based biodetection.[27,28,31]

Exploring the Functional Properties of Interparticle Interactions and Structures

To illustrate the importance of understanding both interparticle and collective properties of the nanoparticle assemblies in a wide range of potential applications, this section highlights a few examples in two areas of our work, including chemical sensing and biosensing.

Chemical Sensing of Nanostructured Interparticle Framework. The interparticle interactions and structures defined by the molecular mediators and templates via covalent (e.g., thiols), hydrogen bonding (e.g., acid-functionalized thiols), ionic (e.g., dicarboxylic acids), or van der Waals interactions (e.g., hydrophobic alkyl chains) all create interfacial or interparticle binding sites for molecular interaction or recognition, which is the basis of chemical sensing. One strategy involves exploring thin-film assemblies of gold nanoparticles (2−5 nm) derived from 11-mercaptoundecanoic acid via hydrogen bonding as a nanostructured ligand framework to mimic ion-gating membranes[57] (Figure 5A), demonstrating ion passages through the nanostructured ligand framework. At low pH, the redox ($[Ru(NH_3)_6]^{3+/2+}$) currents are basically shut off by the film ("closed" state), with only small capacitive currents being detectable. In contrast, the response at the high pH is large ("open" state) because the network carries negative charges ($-CO_2^-$) and admits the positively charged redox species. In contrast to the insignificant mass change at pH 3, a distinctive mass change profile is detected at pH 11 by

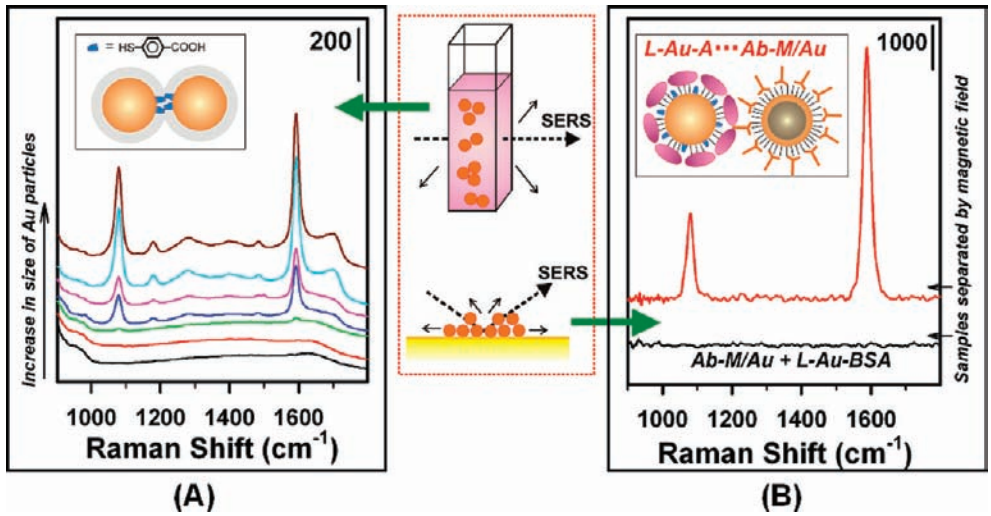

FIGURE 6. SERS spectra showing (A) particle-size dependence for MBA-labeled Au nanoparticles (30, 40, 50, 60, 70, 80, and 90 nm) in an aqueous solution as a result of interparticle interactions and (B) the assembly of Au (80 nm) nanoparticles labeled with Protein A or BSA and MBA- and Au-coated magnetic nanoparticles (~8 nm) labeled with antibody (IgG).

electrochemical quartz crystal nanobalance, suggestive of incorporation of electrolyte species during the reduction of the probe, which, for the reason of electroneutrality, requires the supply of positive charges to compensate the fixed negative $-CO_2^-$ groups. Indeed, the cation flux into the film during the reduction and flux out upon re-oxidation have been found to be sensitive to the atomic mass.[57,58] The fact that the redox responses of the film to $[Fe(CN)]_6^{3-}$ at both pH values were found to be effectively suppressed is consistent with the repulsive effect at the rim of the channels.

Another strategy for exploring the correlation between the interparticle parameters and the functional (electrical and optical) properties[4,12] is demonstrated by the molecularly mediated thin-film assemblies of nanoparticles in chemiresitor sensing arrays[10,12] (Figure 5B). The control of the interparticle spatial properties of alkanethiolate-capped Au and AuAg nanoparticles (2 nm) by a combination of α,ω-difunctional alkyl mediators ($X-(CH_2)_n-X$), such as alkyl dithiols [e.g., dithiol ($HS(CH_2)_nSH$) or dicarboxylic acids ($HO_2C(CH_2)_nCO_2H$)][12] revealed that the chemiresistor response to the sorption of VOCs showed not only a dependence of the sensitivity upon chain length but also the occurrence of a dramatic change of the sensitivity in a region with comparable alkyl mediator and alkyl capping chain lengths. This correlation between the sensing sensitivity and selectivity and the interparticle spatial properties, in addition to the correlation of interparticle molecular mediator lengths with the collective electrical/optical properties,[12,15,16] reflects a balance between the interparticle chain–chain cohesive interdigitation and the nanostructure–vapor interaction, an important insight for the delineation between the interparticle spacing and the nanostructured sensing properties.

Detection of Biomolecular Specificity via Interparticle Spectroscopic Amplification. The use of nanoparticles as a probe for the separation and detection of DNAs or proteins via interparticle amplification of optical and SERS signals provides an advanced paradigm for medical diagnostics. Magnetic nanoparticles coated with a biocompatible layer or gold shell (M@Au) are often desired because it not only provides enhanced stabilization but also allows for fine tuning of the surfaces to impart biocompatibility or the desired chemical and biological interfacial reactivities. The immobilization of biological recognition sites on Au or M@Au and the subsequent recognition of the targeted proteins provide an effective means for the separation of biological molecules.[27,28,31] For example, in the temperature-induced assembly and disassembly processes of DNAs and gold nanoparticles,[37] the introduction of a molecular recognition probe or restriction enzyme leads to intervention of the assembly disassembly process depending upon its specific biorecognition.[56] On the basis of the size correlation of the surface plasmon resonance properties, one example of our work[28,59] in understanding how the coupling of the localized fields between nanoparticles influences the SERS effect[24–26] in solutions involves comparing the SERS spectra for mercaptobenzoic acid (MBA)-labeled gold nanoparticles of different sizes on Au thin-film substrates and stable aqueous solutions (Figure 6A).

The SERS intensity for the solution samples was found to be significant and shows a gradual increase with particle size, which is attributed to the SERS effect from dimer/trimers in the

solution formed via interparticle hydrogen bonding of the adsorbed MBAs. In contrast to the salt-induced uncontrollable and irreversible aggregation, the combination of controlled centrifugation, solution composition, and interparticle interactions could produce stable and small clusters of the nanoparticles (e.g., dimers or trimers) in the solution that exhibit the SERS effect for detection,[28,59] which has implications for further work on understanding the theoretical "hot spot" effect.[24,25]

The size correlation of the SERS effect for nanoparticles in aqueous solutions[28,59] also constitutes the basis for developing SERS and magnetic nanoprobes for bioseparation and detection. One example involves the immobilization of Raman label (L = MBA), Protein A (A) and antibody (Ab) on Au and M@Au (or Ag) nanoparticle surfaces for SERS detection of the Protein-A-antibody-binding activity.[27,28,31] The reaction product between Protein-A-capped Au nanoparticles with a Raman label (L−Au−A) and the antibody-capped M@Au nanoparticles (Ab−M@Au) is separated by applying a magnetic field. The detection of the diagnostic signals of the MBA for the separated product [(L−Au−A)·(Ab−M@Au) pair] in the SERS spectra (Figure 6B) is in sharp contrast to the absence of such signals for the (L−Au−BSA) + (Ab−M@Au) pair derived in a control experiment using bovine serum albumin (BSA) to replace Protein A. A further quantitative delineation of the SERS signals with the concentrations and the nanostructural parameters is part of our ongoing work for the development of magnetic SERS nanoprobes for bioassays.

Concluding Remarks

The combination of the mediator and templating molecular forces provides a paradigm for designing and controlling the interparticle interactions and structures in the molecularly mediated processing and assembly of nanoparticles. In addition to revealing the ability in processing sizes, shapes, and compositions of the nanoparticles, our studies have shown that this paradigm creates opportunities for manipulating the interparticle interaction properties and detecting the molecular signatures. Although most of the understanding of the covalent, electrostatic, hydrogen bonding, multidentate coordination, $\pi-\pi$ interactions, and chiral recognition are based on molecules with specific structures and nanoparticles with gold, alloy, and core−shell structures, the fundamental insights are applicable to studies of the interparticle interactions and structures of other systems with different molecules and nanoparticles. Both noncovalent and covalent interactions in the nanoparticle assemblies are important for manipulating the interparticle properties toward building functional nanostructures. The noncovalent interparticle interactions are useful for manipulating the assembly/disassembly reversibility, whereas the covalent interactions facilitate the assembly of stable nanostructures for fine tuning the chemical sensing sensitivity.

The molecularly mediated assemblies of nanoparticles also open prospects to combine the nanostructure-tuning capabilities with the unique electrical, optical, magnetic, and spectroscopic properties. Although the illustrated examples are in areas of chemical sensing, biomimetic, or biological detection exploiting the nanostructured framework's electrical, optical, magnetic, and spectroscopic properties, the basic principles are expected to be applicable to many other nanoparticle assemblies that are structurally defined for harnessing the nanoscale properties. In all of these aspects, a further detailed delineation of the interparticle design and control parameters should have a profound impact on the exploration of molecularly mediated assembly of nanoparticles for a wide range of technological applications.

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FOOTNOTES

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