Review

Gold nanoparticles functionalized with supramolecular macrocycles

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ARTICLE INFO

Article history:
Received 28 February 2013
Received in revised form 9 April 2013
Accepted 9 April 2013
Available online 18 May 2013

Keywords:
Supramolecular macrocycles
Au nanoparticles
Synthesis
Assembly
Nanomaterials

ABSTRACT

Gold nanoparticles (AuNPs) functionalized with supramolecular macrocycles are versatile and diverse hybrid nanomaterials, which combine and enhance the characteristics of the two components. In this mini-review, we summarize the recent research progress on the synthesis and assembly of AuNPs functionalized with different supramolecular macrocyclic compounds, i.e., crown ethers, cyclophanes, cyclodextrins (CDs), cucurbit[n]urils (CB[n]), calix[n]arenes, and pillar[n]arenes (P[n]A). Meanwhile, applications of these supramolecular hybrid nanomaterials in the fields of sensors, biomedicine and plasmonic devices are also presented.

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1. Introduction

Over the past few decades, nanomaterials have stimulated great interest in both the basic and applied sciences because of their unique physical and chemical characteristics that are substantially different from bulk materials [1]. Amongst them, in particular, gold nanoparticles (AuNPs) feature interesting and useful electronic, optical and catalytic properties that originate from their high surface area to volume ratio and quantum-confined properties [2]. In recent years, AuNPs, possessing high chemical stability, facile synthesis, surface functionalization, biocompatibility, and tunable optical and electronic properties, have led to many promising applications in sensors [3], nanoelectronics [4,5], biomedicine [6], catalysis [7], and surface-enhanced Raman scattering (SERS) spectroscopy [8]. Functionalization of AuNPs with stabilizing ligands possessing amine (–NH₂), carboxyl (–COOH), or sulfhydryl (–SH) groups is very important to protect them from agglomeration, regulates their surface properties, making them possible to form rich hybrid nanomaterials [9–11]. The marriage of AuNPs and supramolecular macrocycles can lead to the birth of novel supramolecular hybrid nanomaterials, which combines and enhances the characteristics of the two components, such as the electronic, thermal, and catalytic properties of AuNPs and molecular recognition of the macrocyclic hosts. This line of research broadens the horizon of nanomaterials, and expands their potential applications in nanosensors [12–16], drug delivery [17–19], separation of fullerenes [20], and ordered supramolecular self-assembly of AuNPs [21].

Supramolecular macrocycles, i.e., crown ethers, cyclophanes, cyclodextrins (CDs), cucurbit[n]urils (CB[n]), calix[n]arenes, and pillar[n]arenes (P[n]A), continue to be central to supramolecular chemistry [22–28]. Many researches have been done on their synthesis, host–guest chemistry, and the construction of novel supramolecular architectures [29,30]. While there are many excellent reviews on both AuNPs and supramolecular macrocycles reported, those focusing on AuNPs functionalized with supramolecular macrocycles are still rare. In this review article, we first give a general introduction to different supramolecular macrocycles-functionalized AuNPs, emphasizing on their synthesis and supramolecular assembly behaviors. We then describe a few representative examples of these supramolecular hybrid nanomaterials for potential and practical applications. The last section will discuss the challenges and opportunities remaining in this field.

2. The preparation and self-assembly of supramolecular macrocycle–AuNP hybrid nanomaterials

The introduction of supramolecular concepts to gold nanomaterials provides a new avenue for the fabrication of hybrid nanomaterials with improved functionalities. Supramolecular macrocyclic compounds can be used as stabilizing ligands for the preparation of AuNPs to enhance their recognition and sensing abilities on material surfaces. On the other hand, the supramolecular self-assembly of macrocycles-modified AuNPs is promising for the formation of morphologically controlled or highly ordered
arrays, which is fundamental for the ultimate miniature device. In this section, we will focus mainly on the preparation and assembly of AuNPs functionalized with crown ethers, cyclophanes, CDs, CB[n], calixarenes, and P[n]A, respectively.

2.1. Crown ether-functionalized AuNPs

In the mid-1960s, crown ethers was first synthesized by Pedersen, which contain hydrophobic exteriors and can form inclusion complexes with cations, especially alkali and alkaline earth metal ions via an ion–dipole interaction [23]. The fields of phase-transfer catalysis, extraction and recovery of heavy metal ions, and anionic synthetic reagents benefited profoundly from this seminal discovery of crown ethers [31,32]. Based on the above properties, Lin et al. designed and synthesized crown ethers-functionalized AuNPs through ligand exchange with 15-crown-5 thiol and used it for the detection of K+ [33]. Upon exposure to K+, the colloidal solution changes from red to blue which was due to aggregation of AuNPs induced by 2:1 sandwich complex between 15-crown-5 moiety and K+. There are two possible binding schemes for 15-crown-5/K+/15-crown-5 sandwich complexation, namely, intraparticle and interparticle association. In the former case, two 15-crown-5 macrocycles from neighboring arms of the same AuNPs bind to one K+, while the latter case, two macrocycles from different AuNPs bind to one K+. Interestingly, Chou et al. synthesized AuNPs functionalized with single 15-crown-5 macrocycle via single molecular exchange technique on SiO₂ nanoparticle, and then successfully constructed dimeric AuNPs through the introduction of K⁺ which forms sandwich complex with two 15-crown-5 macrocycles on two AuNPs (Fig. 1). The association mechanism was deduced and discussed at the molecular level, paving a new way for the construction of controlled self-assembly of AuNP oligomers [13].

2.2. Cyclophane-functionalized AuNPs

Cyclophane-based mechanically interlocked entity was incorporated with AuNPs, as pioneered by Stoddart and Grzybowski et al. [34–36]. They found that, upon their attachment to the surfaces of AuNPs, the redox potentials of mechanically interlocked switches could be affected and AuNPs were also endowed with supramolecular recognition abilities. In their studies, AuNPs were functionalized with [2]pseudorotaxanes comprising of tetraphiafulvalene (TTF) units encircled by cyclodib[paraquat–p-phenylene] (CBPQT⁺) rings. The redox potentials of the TTF unit in 1/2-AuNPs–CBPQT⁺ pseudorotaxanes were more positive after their immobilization than those of 2-AuNPs–CBPQT⁺ in solution [34]. Stoddart and Grzybowski et al. [35] also reported that AuNPs could be self-assembled into dimers, trimers, tetramers via noncovalent bonding interactions between AuNPs decorated with TTF and bridging molecules incorporated multiple CBPQT⁺, i.e., dimer 1⁺, trimer 2⁺, and tetramer 3⁺ as shown in Fig. 2.

2.3. CD-functionalized AuNPs

CDs are a family of cyclic oligomers composed of six, seven, or eight α-d-glucopyranoside units linked by α-1,4-glucose bonds and possess a hydrophobic cavity that can form stable inclusion complexes with a variety of organic substrates in aqueous media [24]. They can be used as appreciable stabilizing ligands to form novel hybrid nanomaterials with AuNPs due to high solubilization ability, low toxicity, and commercial availability with low price. In 1999, Kaifer et al. reported, for the first time, the synthesis of CD-modified AuNPs and investigated their host–guest recognition properties [37]. They capped AuNPs with perthiolated CDs and took advantage of the specific recognition ability of CDs to realize supramolecular network aggregation of AuNPs whose assembly was driven by the ferrocene dimer and C₆₀ molecules, acting as noncovalent molecular linkers between the nanoparticles (Fig. 3) [37,38]. Furthermore, the binding interactions of AuNPs capped with CD macrocycles with cationic ferrocene derivatives can realize the phase transfer of hydrophilic CD-modified AuNPs to low polarity solution phases [39]. Other methods also were applied to synthesize CDs-modified AuNPs [40,41]. For example, Luong et al. synthesized AuNPs by femtosecond laser ablation of a gold metal plate in an aqueous solution of unmodified CDs [41].

Liu and Yang et al. have done extensive work on the synthesis and host-guest properties of CD derivatives, along with the construction of CD-based supramolecular architectures and hybrid nanomaterials [42–47]. A series of functionalized CDs were applied for the preparation and assembly of AuNPs. In 2005, Liu et al. synthesized thio[2-{(benzoylamino)ethylylamino}–β–CD] fragment modified AuNPs which can be used for recycling extractors for [60]fullerene [20]. Meanwhile, CDs-based polyseudorotaxanes, such as mono-6-thio–β–CD polyseudorotaxanes, and L-tryptophan-CD polyseudorotaxanes, were also fabricated to achieve...
bioactive supramolecular assembly of AuNPs [44,45]. In addition, Liu et al. also reported the synthesis of oligo(ethylenediamino)-β-cyclodextrin modified AuNPs, acting as a DNA concentrator [46].

2.4. CB[n]-functionalized AuNPs

CB[n] (n = 5, 6, 7, 8, 10) are pumpkin-shaped, rigid and highly symmetric macrocyclic cation receptors, comprising n glycoluril units. They have gained much attention due to their unique structure and outstanding multiple recognition properties and have been extensively investigated in host–guest recognition properties, the construction of supramolecular architectures, sensors, drug delivery, and biomimetic systems [25]. Recently, Li et al. reported that CB[n] were capable of binding to Au surfaces through the interaction between carbonyl moiety and Au [48]. In 2010, Scherman et al. reported for the first time the preparation of CB[5]-capped AuNPs and examined their dynamic aggregation property in water. After that, AuNPs capped with different sizes of CB[n] (n = 5–8) were synthesized [49,50]. Aggregation of AuNPs with CB[n] would produce a repeatable, fixed, rigid interparticle separation. Scherman and co-workers systematically inspected the sensitive plasmonic evolution along with such assemblies which is important to their uses as powerful surface enhanced Raman spectroscopies (SERS) substrates [51,52].

2.5. Calixarene-functionalized AuNPs

Calixarenes are cyclic basket-like macrocyclic compounds and present thermally and physically robust structures base on phenolic methylene bridged macrocycles. The properties of calixarenes can be adjusted by the modification of the upper and the lower rims, resulting in a wide range of interesting functionalities and possible applications, e.g., phase-transfer agents, ion-channel blockers and biomedicine [22,53,54]. In 1999, Wei et al. reported the use of C-undecyclic[4]-resorcinar-ene and octamethyl derivative to encapsulate and stabilize AuNPs via the chemisorption between Au and O, but their adsorption to the metal surface was too labile to be useful for further manipulations [55]. To deal with this defect, thiolated resorcinarenes were designed and synthesized by Wei et al., which were robust to desorption from the metal surface [56]. Furthermore, resorcinarene tetrathiol-encapsulated AuNPs self-assembled into hexagonally close-packed 2D arrays with good local order (Fig. 4) [21].

2.6. P[n]A-functionalized AuNPs

In 2008, P[n]A, as a new class of supramolecular macrocyclic hosts, were firstly reported by Ogoshi et al. and possess unique symmetric pillar-shaped architectures that is different from the basket-shaped structure of the meta-bridged calixarenes [57]. Huang, Hou, Li, Ogoshi, Stoddart, Wang, and our research group have done extensive work on the synthesis of P[5]A and its derivatives, their host–guest chemistry, construction of supramolecular polymeric architectures, and the development and applications of P[5]A-based novel supramolecular materials [58–64]. Recently, our group developed an effective trifluoromethanesulfonic acid-catalyzed cyclooligomerization strategy for the synthesis of functionalized P[5,6]A and co-P[5,6]A and investigated its reaction mechanism of solution-phase catalytic synthesis [64]. Hou et al. reported a class of artificial transmembrane amino acid channels from peptide-appended P[n]A (n = 5, 6) [61]. Stoddart et al. incorporated an A1-A2-difunctionalized P[5]A into a metal-organic framework [60]. It is worth noting that the conjugation of P[n]A with AuNPs is also extremely important for the development of P[5]A-based novel hybrid nanomaterials. Huang et al. applied a new water-soluble P[5]A with ten imidazolium groups at its two rims as stabilizer for the preparation of AuNPs which showed good catalytic activity [65]. Very recently, our group reported the synthesis of carboxylatopillar[5]arenic sodium salts (CP[5]A), a new water-soluble macrocyclic synthetic receptor, and employed CP[5]A as a superb stabilizing ligand for in situ preparation of AuNPs. Their supramolecular self-assembly mediated by viologens I and II was also investigated, and the hybrid nanomaterials showed excellent properties for herbicide detection which will be detailed in the following section (Fig. 5) [16].

3. Properties and applications of AuNPs functionalized with supramolecular macrocycles

AuNPs have experienced a renaissance driven by decorating the surface with functional molecules. The conjugation of AuNPs and supramolecular macrocycles significantly combines and enhances...
the characteristics of the two entities, such as the electronic, thermal, and catalytic properties of AuNPs and molecular recognition of the macrocyclic hosts, opening interesting perspectives on sensors, biomedicine, plasmonic devices, and etc. In this section, we will give a brief introduction to the applications of supramolecular macrocycle-functionalized AuNPs in these research fields.

3.1. Sensors

The assembly or disassembly of AuNPs induces the shift of their plasmon resonances, resulting in a visible color change to yield a detectable response signal. Supramolecular macrocycle-functionalized AuNPs possess greater advantages, providing multiple interaction sites and allowing for specific interactions with analytes. For example, Velders et al. reported supramolecular assembly of CB[7]-functionalized AuNPs as optical probes for enzyme-linked immunoassays and multivalent β-CD-decorated AuNP networks as ultrasensitive enzyme sensors [14,15]. Blanco et al. reported new electrochemical sensing platforms fabricated by the absorption of CB[6] and CB[7] on gold [66]. Our research group applied CP[5]A-modified AuNPs as optical probes for herbicide detection. A small amount of viologen I (paraquat) can cause the aggregation of CP[5]A-modified AuNPs in a short time, along with a spectral change that was proportional to the mount of the paraquat [16]. In addition, we envision that CP[5]A can induce aggregation as well as form hot spots between two or more AuNPs from rigid macrocyclic structures. Molecules selectively recognized by CP[5]A is subjected to intense field enhancement at the heart of the plasmonic hot spot. So, SERS-based nanosensors based on CP[n]A-modified AuNPs, with enhanced selectivity and sensitivity, are currently under construction in our laboratory.

3.2. Biomedicine

AuNPs possess a range of properties such as chemical inertness, low toxicity and good biocompatibility, which satisfies their application in biomedicine. The combination of AuNPs and supramolecular macrocycles has great potential in drug delivery and hyperthermal therapy. Heo et al. reported a complex AuNPs platform that included biotin as a targeting ligand, paclitaxel (PTX) as an anti-cancer drug, Rhodamine B to facilitate fluorescence detection, and PEG for enhanced biocompatibility, as shown in
Fig. 6 [18]. CDs were attached to the surface of AuNPs for the inclusion of noncovalent PTX, which can then be effectively released from the complex AuNPs platform. Cell viability analyses showed that the complex AuNPs platform was effective for drug delivery. Rotello et al. presented a host–guest system that includes complementary diaminohexane-terminated AuNPs (AuNP–NH₂) and CB[7] to form a non-toxic assembly that is readily taken up by cells. CB[7] can be removed by the presence of 1-adamantylamine (ADA), causing the endosomal release and concomitant *in situ* cytotoxicity of AuNP–NH₂ [19].

Fig. 5. Schematic representation of the formation of CP[5]A-modified AuNPs and their supramolecular self-assembly upon addition of guest viologen molecules (I and II).

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Fig. 6. Schematic depiction of AuNPs functionalized with biotin, Rhodamine and PTX.

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3.3. Plasmonic devices

The nanoscale movements of molecular switches constructed by supramolecular macrocycles can influence plasmon resonances of AuNPs, which can be used as the active components in plasmonic devices. As shown in Fig. 7, Zheng et al. presented a Au nanodisk array coated with bistable, redox-controllable [2]rotaxane molecules, consisted of a long, dithiolane-terminated thread incorporating two electron-rich recognition units – tetrathiafulvalene (TTF) and 1,5-dioxyanthraquinone (DNP) – which is encircled by the electron-deficient macrocyclic ring, CBPQT++. In the ground state of 2++, the CBPQT++ ring resides preferentially at the TTF station. Upon oxidation of the TTF station, however, the CBPQT++ ring loses its affinity for the now oxidized TTF2++ on account of the Coulombic repulsion, and moves to the DNP station. The two co-conformations have markedly different electronic properties and extinction spectra (Fig. 7c) [4]. A maximum change of SPR was observed by rationally designing the size of Au nanodisk.

![Diagram](image-url)
4. Conclusions and outlook

This mini-review summarizes the synthesis, assembly and applications of AuNPs functionalized with different supramolecular macrocycles, i.e., crown ethers, cyclodextrins, CDs, CB[n], calixarenes, and P[n]A. We envision other types of supramolecular macrocycles will also be employed for the surface functionalization of AuNPs and show more potential applications in different fields very soon [67]. The development of supramolecular chemistry has advanced from the investigations of the basis of host–guest recognition to the construction of novel supramolecular architectures, e.g., molecular switches, supramolecular polymers and hybrid nanomaterials. The powerful combination of supramolecular macrocycles and AuNPs paves the way for the improvement of performance of hybrid nanomaterials. While appreciable progress has been made in terms of their synthesis, assembly and applications, greater space needs to be explored, e.g., (a) the precise control of the numbers of macrocyclic compounds per AuNP, leading to more accurate sensor detection; (b) the effective use of thermal properties of AuNPs and molecular recognition of the macrocyclic host for the development of novel drug delivery systems; (c) deeper understanding of fundamental principals of supramolecular self-assembly to help achieve morphologically controlled and highly ordered arrays of AuNPs for effective device fabrication. We believe that the combination of supramolecular macrocycles and AuNPs would have a very exciting and bright future in the world of nanomaterials.

Acknowledgments

We thank the National Natural Science Foundation of China (No. 21272093), the Research Fund for the Doctoral Program of Higher Education of China (No. 20120061120117), and the Independent Innovation Research Program from the State Key Laboratory of Supramolecular Structure and Materials for financial support.

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