LITERATURE REVIEW

Controlled spontaneous generation of gold nanoparticles assisted by dual reducing and capping agents

Frédéric Dumur · Audrey Guerlin · Eddy Dumas ·
Denis Bertin · Didier Gigmes · Cédric R. Mayer

Introduction

During the last decades, noble-metal nanoparticles have attracted a great deal of interest by their unique optical, electronic, magnetic, and catalytic properties and intense research efforts are still devoted to develop new synthetic and functionalizing strategies [1–5]. This extremely active research field was supported by the amazing chemical and physical properties displayed by the metal particles of nanometric size that are markedly different from those of the corresponding bulk materials [6]. Especially, optical and electronic properties of metal nanoparticles can be easily tuned by modifying their size and shape [7]. Regarding noble metals nanoparticles, gold nanoparticles (Au-NPs) are without contest at the forefront in this research area. Academic interest for Au-NPs, which showed fast growth over the past years, is motivated by the strong surface plasmon resonance displayed by gold nanoparticles. In addition, gold nanoparticles gained a renewal of interest by finding potential uses in medical diagnostics, imaging, and therapeutic treatments. In these last fields, preparation of Au-NPs with benign reactants is often favored to remove all potential contamination of the colloidal solutions [8–14]. To date, four different classes of biological applications for Au-NPs have been identified: labeling, delivering, heating, and sensing [15]. However, the use of gold nanoparticles was not limited to biological applications and Au-NPs were also successfully employed as scaffolds for molecular recognition of elements and molecules [16], in optoelectronics and data storage [17], in nanotechnology with molecular switches [18] and motors [19], or in light-harvesting assemblies [20, 21]. Typically, gold nanoparticles are obtained by chemical reduction of tetrachloroauric acid [22, 23]. However, this conventional approach is based on the use of external chemical reductants that often produce undesired side-products. Therefore, a series of functionalizing agents for Au-NPs has recently been developed that display a dual role of effective reducing agents of gold salts and of stabilizers, by providing a robust coating to gold nanoparticles, within a unique reaction step. Seven different types of these reducing/capping agents were investigated to date: microorganisms and bacteria, plants extracts and physiological molecules, inorganic reagents and metal complexes, organic molecules, organic acids and salts, liposomes, and polymers (Table 1). In this review, we propose to focus on these exciting functionalizing agents exerting the dual role of reducing and coating agents and to discuss the precise size-controlled synthesis of Au-NPs using this approach.

F. Dumur (✉) · D. Bertin · D. Gigmes
Laboratoire Chimie Provence, UMR 6264 CNRS, équipe CROPS,
case 542, Universités d'Aix-Marseille I, II, III,
Faculté des Sciences et Techniques de Saint Jérôme,
Avenue Escadrille Normandie-Niemen,
13397 Marseille Cedex 20, France
e-mail: frederic.dumur@univ-provence.fr

A. Guerlin · E. Dumas · C. R. Mayer (✉)
Institut Lavoisier de Versailles, UMR 8180 CNRS,
Université de Versailles Saint Quentin en Yvelines,
45 avenue des Etats-Unis,
78035 Versailles Cedex, France
e-mail: cmayer@chimie.uvsq.fr

Discussion

The generation of stable colloidal suspensions with particles of controlled size and shape requires a real synthetic strategy as well as a perfect knowledge of the intimate

Table 1 Reducing/capping agents used to synthesize spherical Au-NPs

	Agents	Particles size (nm)	Mean size (nm)	Ref.
1	Black Darjeeling tea	24 to 48	35±7	[24]
2	Phyllanthin	18 to 38	29	[25]
3	Henna	7.5 to 23	12.5	[26]
4	*Terminalia catappa*	10 to 35	29	[27]
5	*Emblica officinalis*	15 to 25	–	[28]
6	*Tamarindus indica*	–	–	[29]
7	*Mucuna pruriens*	6 to 17.5	12.5	[30]
8	*Rhodopseudomonas capsulata*	10 to 20	–	[31]
9	Korean red ginseng	2 to 40	16±3	[32]
10	*Centella asiatica*	2 to 22	9.3	[33]
11	Coriander	6.7 to 57.9	20.6±7	[34]
13	Red grape pomace	5 to 10	–	[36]
14	*Cinnamomum camphora*	12 to 37	21.5	[37]
15	*Volvariella volvacea*	–	25	[38]
16	*Rhizopus oryzae*	–	9.52±0.26 42.63±1.98	[39]
17	Lemongrass	100 to 200	–	[40]
18	Soybean extracts	10 to 25	15±4	[41]
19	Bayberry tannin	1 to 3	1.8±0.3	[42]
20	α-Amylase	5 to 20	–	[43]
21	Living alfalfa plants	2 to 20	13±2	[44]
22	*Chilopsis linearis*	2.9 to 17.2 Å	–	[45]
23	*Sesbania drummondii*	6 to 20	–	[48]
24	*C. linearis* + SCN$^-$	–	0.55	[49]
25	*Desulfovibrio desulfuricans*	–	–	[53]
26	*D. desulfuricans*	5 to 50	–	[54]
27	*R. capsulata*	10 to 20	–	[57]
28	*Shewanella algae*	10 to 20	–	[61]
29	*Rhizopus oryzae*	–	10	[62]
30	*Aspergillus niger*	–	4 (pH>7) 18 (pH=7)	[63]
31	*Rhodobacter capsulatus*	2 to 34	13	[64]
32	*Rhodococcus* species	5 to 15	9	[65]
33	*Escherichia coli*	30 to 100	–	[66]
34	*Lactobacillus*	20 to 50	–	[67]
35	*Fusarium oxysporum*	8 to 40	–	[68]
36	*Pyrobaculum islandicum* Fe(III)	–	–	[69]
37	*Brevibacterium casei*	–	50	[70]
38	*Verticillium* sp.	–	20±8	[71]
39	*Colletotrichum* sp.	8 to 40	–	[72]
40	*Sargassum wightii*	8 to 12	11	[73]
41	*Thermonospora* sp.	7 to 12	8	[74]
42	*Shewanella oneidensis*	5 to 10	8.4±0.7	[75]
43	Bile salts	4 to 30	10	[76]
44	Bovine serum albumin	–	2	[77]
45	Cholesterol phenoxy hexanoate	12 to 16	–	[79]
46	Cucurbit[7]uril	6 to 22	10±1.6	[80]
47	Thiacalix[4]arene	–	13.5	[81]
48	β-Cyclodextrin	60 to 100	–	[82]
49	Hydroquinone	17 to 25	20	[83]
50	2,3,5,6-Tetrakis-(morpholinomethyl)hydroquinone	–	170±17	[84]

Table 1 (continued)

	Agents	Particles size (nm)	Mean size (nm)	Ref.
51	Oleylamine	8 to 12	10±0.6	[85]
52	Oleylamine	18 to 25	21	[86]
53	Oleylamine	15 to 23	20	[87]
54	Hexadecylamine	4.5 to12	–	[88]
55	*Bis*(amidoethyl-carbamoylethyl) octadecylamine	20 to 250	–	[89]
56	4-Hexadecylaniline	–	4.2±0.6	[90]
57	*Bis*(2-(4-aminophenoxy) ethyl)ether	3 to 6	–	[91]
58	4-Aminothiophenol	–	3	[92]
59	Dodecylaminomethanol	2 to 10	4.5	[93]
60	Dodecylaminomethanol	1.5 to 5	3.9±0.5	[94]
61	Tween 80	–	3.02±0.52	[95]
62	β-Glucose	5 to 13	–	[97]
63	Honey (fructose)	–	15	[98]
64	1-Pyrenemethylamine	–	15.6±2.1	[99]
65	Luminol	8 to 19	13	[100]
66	Lauroyl glucose and fructose lauroyl ascorbate	168 to 226 35 to 48	193 39	[102]
67	Tyrosine	–	45	[103]
68	Alkylated tyrosine	5 to 100	42±13	[104]
69	Aspartic acid	17 to 33	24±3	[105]
70	Tryptophan	–	31.2±1.8	[106]
71	Glutamic acid	10 to 15	–	[107]
72	Glutamic acid	–	40±2	[108]
73	Tryptophan-based amphiphiles	10 to 60	–	[109]
74	L-Tyrosine	5 to 40	–	[111]
	Glycyl-L-tyrosine	5 to 30	–	
	L-Tyrosine + glycyl-L-tyrosine	13 to 30	–	
75	Lysine	–	6±2	[112]
	Arguinine	–	10±5	
	Tryptophan	–	60±5	
76	Tannic acid	12 to 58	–	[113]
77	Tannic acid	–	–	[114]
78	Ascorbic-acid-based amphiphiles	11 to 18	–	[115]
79	Gallic acid	–	–	[117]
80	2-Mercaptosuccinic acid	–	10	[118]
81	2-Mercaptosuccinic acid	30 to 150	–	[119]
82	Lactic acid	–	–	[120]
83	Cinnamic acid	–	15	[121]
84	Ciprofloxacin	–	20	[122]
85	Cephalexin	50 to 80 120 to 200	–	[123]
86	Cefaclor	15 to 26	23±2	[124]
87	Dextran	10 to 18	13.6±1.4	[125]
88	Trisodium citrate	20 to 40	–	[129]
89	Sodium alginate	2 to 30	8±2	[130]
90	Poly(sodium acrylate)	5 to 65	–	[131]
91	Sodium acrylate	11 to 17	14	[131]
92	Choline- and purpurin-18 based ionic liquids	8 to 25	14	[132]
93	Phosphatidylcholine	–	4.13/25.1	[133]
94	Monoolein	35 to 105	–	[134]
95	Ethosomes bilayers	3 to 16 12 to 24	8 20	[135]

Table 1 (continued)

	Agents	Particles size (nm)	Mean size (nm)	Ref.
96	Poly(ethylene oxide) (POE)	–	17	[137]
97	Diamine-terminated POE	–	16.3	[138]
98	Polyethyleneimine (PEI)	–	15	[139]
99	Poly-(propyleneimine) dendrimers	4 to 33	–	[140]
100	Polydimethylsiloxane	20 to 70	–	[141]
101	Polydimethylsiloxane	7 to 13	–	[142]
102	Polyvinylpyrrolidone	–	10.0±1	[143]
103	Polyvinylpyrrolidone	2 to 3	–	[144]
104	Polyvinylpyrrolidone	–	18.8±3	[145]
105	Poly(allylamine)	1.2 to 3.4	1.7±0.6	[146]
106	Poly(allylamine) hydrochloride	5 to 15	–	[147]
107	Polystyrene	–	3.0±2.0	[148]
		–	10.0±5	
108	Polyaniline	–	20	[149]
109	Glycerol	–	6.9±0.1	[150]
110	Block-PEO-block-PPO-block-PEO	–	8.3 (P103)	[152]
			11.3 (F127)	
111	Block-PEO-block-PPO-block-PEO	7 to 20	–	[153]
112	Double hydrophilic block copolymers	–	25	[154]
113	R-biotinyl-poly(ethyleneglycol)-block-[poly(2-(N,N-dimethylamino)ethyl methacrylate)]	6 to 13	–	[155]
	PCA–PEG–PCA	5 to 10	–	[156]
114	Poly(o-phenylenediamine)	5 to 50		[157]
115	Poly(o-phenylenediamine)	50 to 100	–	[158]
116	Poly(o-phenylenediamine)	–	5	[159]
117	Polyaniline	30 to 40	–	[160]
118	Polyaniline	10 to 50	–	[161]
119	Polyaniline	10 to 50	–	[162]
120	Poly(o-anisidine)	<4	–	[163]
121	Poly(o-aminophenol)	<5	–	[164]
122	Single-walled carbon nanotubes	50 to 550	–	[165]
123	Polypyrrole nanotubes	–	13/80	[166]
124	PEGylated nanogels	–	6	[167]
125	Gum arabic	16 to 45	21.1±4.6	[168]
126	Gellan gum	–	13±1	[169]
127	Gellan gum	13 to 19	–	[170]
128	Sophorolipids	–	10	[171]
129	Carbon nanofibers	7 to 15	–	[172]
130	C_{60} dianions	–	17	[173]
131	Fe(III)-citrate complex	<50	–	[175]
132	Ammonia borane complex	6 to 11	8	[176]
133	$[Ir(dfppy)_2(FluoDT(S^-)_2)]^+$	–	3–4	[177]
134	$SiW_{12}O_{40}$	–	13.1±3.9	[178]
135	$H_3PW_{12}O_{40}$	–	35±3	[179]
136	$Na_2[Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3(Hnta)_3]$	–	9.5±0.5	[181]

relationship existing between the surface of the particles and the stabilizing agent. In this regard, the growth of gold nanocrystals persists as long as the crystallization sites are not blocked by the capping agent and as long as the gold (III) salt is available in the reaction medium. In order to obtain Au-NPs of nanometer size, surfactants are introduced in the reaction medium to contain the crystal growth (see Fig. 1). For an efficient entrapment of gold nano-
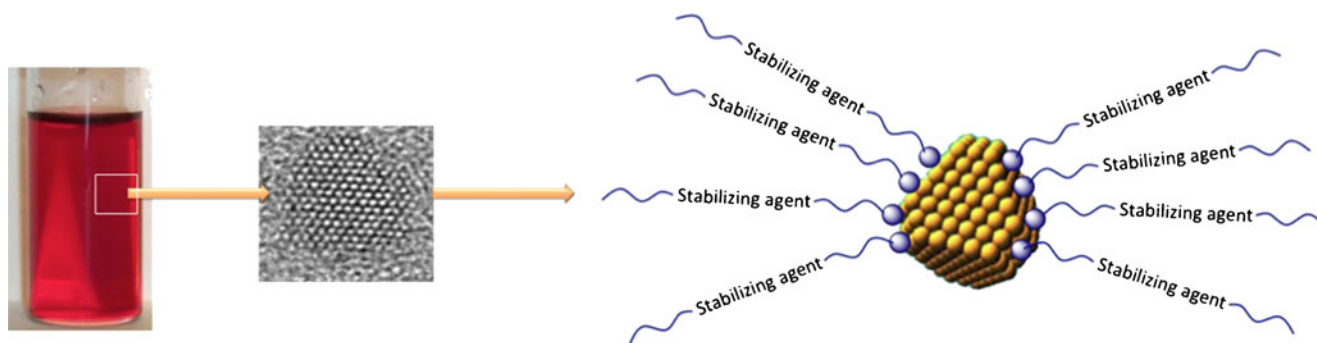
Fig. 1 A colloidal solution of Au-NPs and the schematic representation of a nanoparticle stabilized by a stabilizing agent

crystals, surfactants should display a higher affinity for the surface of the nanoparticle than the solvent molecules but also subsequently act as a stabilizer preventing the aggregation of the particles. Therefore, coating agents are exerting a critical role by passivating the surface. Among its main characteristics, surfactants should not only exhibit a high solubility in the reaction medium but also induce mutual repulsions between particles. Two basic modes of stabilization can be cited (see Fig. 2). The first one is based on the generation of electrostatic repulsion forces between particles which repel each other by establishing a charged coating at the surface of the particles. The second strategy makes use of nonionic bulky surfactants that generate steric repulsions between particles by forming a sterically hindered coating surrounding the surface of the nanoparticles. The high affinity of surfactant molecules for the surface of Au-NPs surfaces finds its origin in the main principles of the coordination chemistry. Molecules of surfactants behave with each individual gold atom at the surface of the particles in a similar way to that observed with ligands and electro-deficient metal ions in metal complexes. Therefore, a prerequisite for surfactants is to possess at least one atom or a functional group exhibiting lone pair electrons that can ensure its binding to the gold particles (see Fig. 3). In the context of this review, surfactants act both as reducing and capping agents.

Plants extracts and physiological molecules

Among all reported reducing/capping agents, plants extracts were seen as a possible eco-friendly approach for the synthesis of Au-NPs (see Fig. 4). Phytochemicals coming from black Darjeeling tea leaves [24], phyllanthin [25], apiin from *henna* leaves [26], leaf extract of *Terminalia catappa* [27], *Emblica officinalis* (Indian Gooseberry) fruits [28], *Tamarindus indica* leaf [29], plants extracts from *Mucuna pruriens* [30], cell-free extract of *Rhodopseudomonas capsulata* [31], Korean red ginseng root (*Panax ginseng* C.A. Meyer) [32], leaves extracts of *Centella asiatica* [33], coriander [34], *Aloe vera* [35], or a waste product of the wine industry, i.e., red grape pomace [36] were notably used. In most cases, natural extracts were often broths obtained from boiled fresh plants leaves. It can be pointed out that all the recent reports concerning the synthesis of Au-NPs via the phytochemical approach were accompanied of investigations examining the cytotoxicity of Au-NPs in terms of proliferation of cells or apoptose [32]. When used in bioreductive synthetic approaches, the concentration of the natural extracts was a crucial parameter for the control of the size and shape of the nanoparticles, as evidenced with apiin [26]. In that case, an increase of the concentration of apiin extract in the reaction medium modified the morphology of the particles, namely from

Fig. 2 Both possible modes of stabilization of gold nanoparticles. **a** Stabilization by electrostatic repulsions and **b** stabilization by steric repulsions
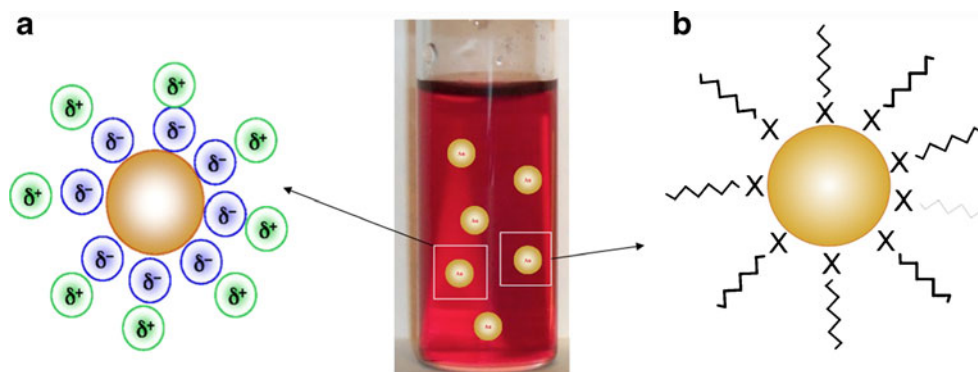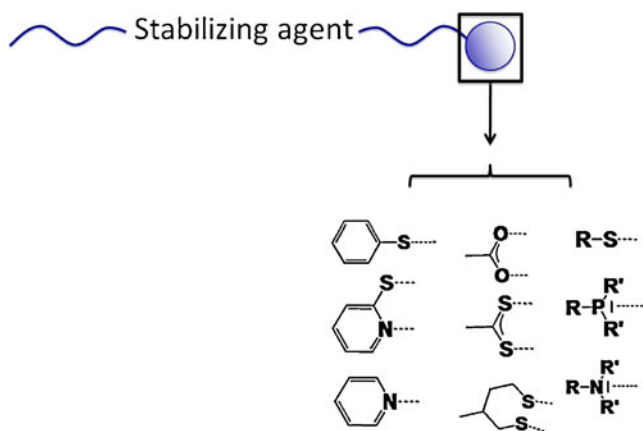
Fig. 3 A series of functional end-groups commonly used for capping agents

predominantly spherical particles to triangular ones. Likewise, *R. capsulata* provided spherical Au-NPs at low concentration whereas nanorods were obtained at high concentration [31]. Contrarily, when purified phyllanthin [25], *Cinnamomum camphora* leaf [37] or edible mushroom *Volvariella volvacea* [38] extracts were employed, progressive increase of the concentration successively produced hexagonal, triangular, and spherical shape forms. Recently, cell-free mycelial extract of *Rhizopus oryzae* enabled the selective preparation of particles of different shapes (spheres, triangles, hexagons, pentagons, stars, and wires) simply by manipulating the key-growth parameters (gold salt concentration, pH of the solution, and reaction time) [39]. By fine-tuning the reaction conditions, synthesis of gold nanoparticles at pH=7 and 30°C for 6 h produced well-dispersed and essentially spherical particles with an average size of 9.52±0.26 nm whereas the same reaction performed at pH=10 and higher concentration of the gold solution for 10 h furnished spherical particles of 50 to 70 nm diameter. Even if highly controlled syntheses of spherical nanoparticles have recently been reported [39], most of these approaches provided relatively polydispersed Au-NPs. The temperature was also determined as a critical parameter for controlling the size and shape of Au-NPs. An elevation of the temperature resulted in a decrease of the average particle size with extracts from black Darjeeling tea

leaves, for which the diameter of the particles evolved from 35 to 24 nm [24]. In another example, when the temperature was increased in the presence of leaf extract of lemongrass, the morphology of the resulting particles changed from triangular to spherical [40]. Authors also demonstrated the shape-directing role of halide ions in the growing process since Cl^- ions promoted the growth of nanotriangles at room temperature, whereas I^- ions favored the formation of spherical nanoparticles in the same conditions. The cooperative reduction of phytochemicals issued for soybean extracts efficiently reduced sodium tetrachloroaurate in aqueous media and produced particles of relatively small size (15±4 nm) [41]. In this interesting example, saccharides (sucrose and stachyose) from soybean were synergistically used to reduce the gold salt whereas proteins (isoflavones and phyto-estrogens) of soybeans provided a strong coating to the particles, thus preventing their sintering. When red grape pomace, a waste product of the wine industry, was used as a reducer, high concentration of polyphenolic compounds enabled to reduce and stabilize quasi-monodisperse spherical particles [36]. The same experience performed with the red wine-produced quasi-spherical Au-NPs in the 10–30 nm range with a few rods, evidencing a lower concentration of polyphenols in wine compared with pomace. Recently, another polyphenol-based natural plant extract, bayberry tannin, also served as a reducing agent and stabilizing agent of Au-NPs in water [42]. By using strict synthetic conditions and by markedly increasing the concentration of bayberry tannin, particles with a mean diameter as small as 1.8±0.3 nm were obtained. Common specificity of polyphenols in tannins is that their molecular backbone is generally composed of rigid aromatic rings functionalized by multiple *ortho*-phenolic hydroxyl groups. Reaction with Au(III) enables the oxidation of the phenolic hydroxyls to the corresponding benzoquinones. More precisely, reduction of Au(III) is initiated by the formation of five-membered ring chelates between the electrophilic metal ion and the phenolic hydroxyls which inductively decompose upon oxidation to the corresponding benzoquinones. Enzymatic activity was also envisioned as another bio-based method for the synthesis of metal nanoparticles. In this aim, enzymatic

Fig. 4 Plant extracts as an environmentally acceptable route for the synthesis of Au-NP
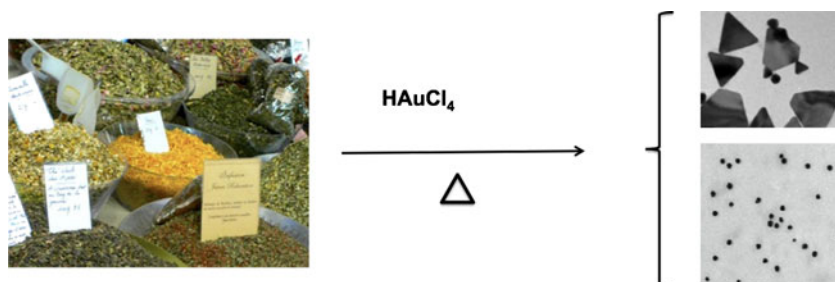
activity of α-amylase for the synthesis of Au-NPs was investigated [43]. Interestingly, if authors tested other enzymes, the reduction process of the parent cationic salt was only observed with pure α-amylase and *Eco*RI and activities of enzymes were maintained after their anchorage to Au-NPs. Careful structural analyses of both enzymes revealed the presence of free SH groups in the side chain of cysteine, certainly involved in the reduction process, and not detected on the other enzymes. Interestingly, thiol groups were positioned on the opposite side of the enzymatic site therefore retaining the biological activity of both enzymes after attachment to Au-NPs.

The synthesis of particles in the sub-100 nm size regime was not only limited to plants extracts but was also investigated from the point of view of living plants. The first report concerning this biosynthetic approach for the stabilization of spherical Au-NPs was published in 2002 by Gardea-Torresdey et al. with living *alfalfa* plants [44]. When *alfalfa* plants were grown in an $AuCl_4^-$ rich environment, gold uptake from solid media by the plants occurred and growth of Au nanoparticles inside the plant was evidenced. Discrete nanoparticles of 2–20 nm in diameter were obtained. This synthesis of Au-NPs related from phytomiming strategies [45], paved way for further investigations [46, 47]. Desert willow (*Chilopsis linearis*) [45] and leguminous shrub (*Sesbania drummondii*) [48] displayed high capabilities to uptake gold from a gold-enriched medium and particles were obtained with sizes ranging from 2.9 to 17.2 Å and 6 to 20 nm, respectively. The size of the particles could be drastically reduced to 0.55 nm in the case of *C. linearis* by adding thiocyanate ions in the reaction medium [49]. Unequivocally, all these studies demonstrated the involvement of proteins, polyphenols, and carbohydrates in the growth process and the stabilization of Au-NPs in living organisms, even if the elucidation of the exact mechanisms involved in the growth of the nanoparticles needs much more experimentations for a complete understanding.

Microorganisms and bacteria

Microorganisms have also been studied for the stabilization of nanoparticles (see Fig. 5). The biosynthesis of spherical Au-NPs by microorganisms has emerged as a safe and reliable alternative competing with the conventional chemical syntheses. The regulation of crystal morphology by proteins is also the central feature that governs the formation of hard tissues such as bones, teeth and mollusk shells. Bacteria are well-known to exhibit high metal reducing capacities and to stabilize particles by biosorption. Notably, carboxylic groups in the cell wall are strong sorption sites for metals [50]. The reducing properties of bacteria are highly pH-dependent [51–57] and reduction of gold salts is reported under aerobic and anaerobic conditions. Concerning this living approach, Beveridge and co-workers demonstrated for the first time in 1980 that Au-NPs could be readily precipitated within bacterial cells of *Bacillus subtilis* with particles sizes ranging from 5 to 25 nm [50, 58–60]. Then, a number of different genera of fungi were investigated in the effort of developing efficient size-controlled syntheses. Mesophilic anaerobic bacterium *Shewanella algae* was able to reduce a gold salt within 30 min at 25°C and pH=7 with the assistance of hydrogen gas as an electron donor [61]. Spherical Au-NPs of 10–20 nm were obtained in the periplasm space. The authors demonstrated the exceptional reducing ability of *S. algae* as the reducing power of 3.2×10^{15} cells/m^3 of the microbial solution at 25°C was comparable to that of a 20-mol/m^3 aqueous solution of citric acid at 50°C. Similarly, native *R. oryzae* strain furnished well-dispersed particles (with an average diameter of 10 nm) with no conspicuous agglomeration. Nanoparticles formed on the mycelia surface were stable up to 6 months [62]. Through severe adjustments of the experimental conditions, filamentous fungus *Aspergillus niger* exclusively formed spherical Au-NPs in alkalin (4 nm) and neutral (18 nm) media by means of proteins localized on the fungal cell walls [63]. Other bacteria such as *Rhodobacter capsulatus* [64], *R. capsulata* [57], actino-

Fig. 5 Microorganisms and bacteria as nanoreactors to produce Au-NPs
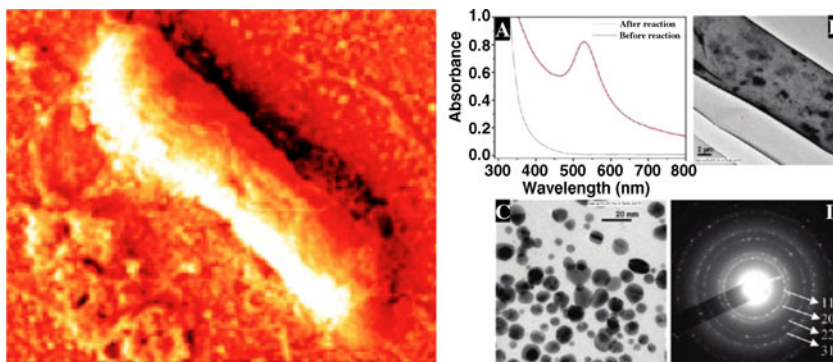
mycete *Rhodococcus* species [65], *Escherichia coli* [66], *Desulfovibrio desulfuricans* [53, 54], *Lactobacillus* strains [67], *Fusarium oxysporum* [68], *Pyrobaculum islandicum* and other hyperthermophilic Fe(III)-reducers [69], and *Brevibacterium casei* [70] were also used to synthesize nanoparticles intra- or extracellularly. The determination of the amino acid sequences of polypeptides involved in the reduction mechanism of Au(III) in living microorganisms was performed with one of the simplest organisms known in nature, i.e., *E. coli* [66]. Careful examination of the proteins revealed the presence of polypeptides that accelerate the rate of colloid appearance by the presence of a catalytic site that functions by acid catalysis and participate to the alteration of the crystal shape. In the presence of these "accelerators," specific direction of crystal growth were favored and other structures such as thin and hexagonal crystals were found in addition to nanospheres.

The first use of eukaryotic organism, *Verticillium* sp. (AAT-TS-4), was reported in 2001 and generated Au-NPs with an average diameter of 20 nm, the smallest particles being located on the cell walls and the largest ones within the fungal cells [71]. In the case of Au-NPs synthesized using the endophytic fungus *Colletotrichum* sp., isolated from geranium leaves, particles were predominantly spherical and aggregated into larger irregular structures with no well-defined morphology. The shape was only poorly controlled using this microorganism [72]. Review of the literature revealed that algae have been only scarcely explored as living nanofactories. Au-NPs with good monodispersity were obtained with marine alga *Sargassum wightii* and small spherical particles ranging from 8 to 12 nm were obtained [73]. This selectivity was comparable to that observed with the extremophilic actinomycete *Thermonospora* sp. [74]. Intracellular precipitation of nanosized particles was also evidenced in respiring bacterium *Shewanella oneidensis* and similar particle sizes were obtained with living and heat-killed cells [75].

Keeping in mind the biological perspectives, less attention has been paid to molecules from biological origin. However, sodium salts of the amino acids conjugates of bile salts successfully produced gold clusters surrounded by a shell of amino acids [76]. Presence of amino and carboxylic groups on amino acids (taurine and lysine) formed anchoring points that strongly bind to the surface of the nanoparticles. Interestingly, an increase of the concentration of amino acids leads to the formation of small particles (4 to 30 nm) which ripen to form larger particles such as triangles and hexagons. Similarly, bovine serum albumin provided small Au-NPs of 2 nm after 12 h of reaction which slowly evolved to form nanoplates after 48 h of reaction [77]. Previously, investigation on three different proteins, namely, bovine serum albumin, Rituximab and Cetuximab revealed that bovine serum albumin was the

only protein of the three able to reduce the gold salt to form gold nanotriangles [78]. A series of cholesteryl phenoxy hexanoate mesogens were also investigated and the influence of the functional group on the meta-position of the phenyl ring was determined. The self-reduction of $HAuCl_4$ was only observed for mesogens bearing amino and carboxylic acid groups [79]. Amino-substituted mesogens ensured the formation of Au-NPs with an average size of 12–16 nm whereas carboxy-substituted mesogens stabilized small Au-NPs with size ranging from 2 to 6 nm.

Organic molecules

Macrocycle cucurbit[7]uril was used to form spherical Au-NPs in the presence of sodium hydroxide [80]. Interestingly, the nanoparticles thus obtained showed strong catalytic activities for the reduction of 4-nitrophenol in the presence of $NaBH_4$. Similarly, reaction of $HAuCl_4$ with thiacalix[4] arene produced nanoparticles whose shapes were finely tuned by controlling the addition of $HAuCl_4$ [81]. This macrocyclic approach was also transposed to cyclic oligosaccharide β-cyclodextrin which formed spherical Au-NPs only in aqueous solutions free of dodecyltrimethylammonium bromide [82]. The organic molecule acting as reducing agent is indeed oxidized during the synthetic process. An illustration is given by hydroquinone that is oxidized in benzoquinone during the synthesis of Au-NPs [83]. The stabilization of Au-NPs by benzoquinone proved to be highly pH-sensitive and stable nanoparticles were only obtained while maintaining the pH below 4. Previously, a more sophisticated hydroquinone derivative, i.e., 2,3,5,6-tetrakis(morpholinomethyl)hydroquinone produced spherical Au-NPs with aggregates as large as 170±17 nm [84]. The preparation of water-soluble Au-NPs is of utmost importance for various applications, for example for biological applications, and several amines were investigated for this purpose. Remarkably, oleylamine (9-octadecenylamine) enabled to form and stabilize well-dispersed Au-NPs by mean of an intermediate Au-amine complex which undergo a rapid thermal decomposition in water to produce Au-NPs [85–87]. Notably, the size of the particles was strongly affected by the amine concentration, and only scarcely by the reaction time. A careful survey of the literature showed that other amines such as aliphatic amines (hexadecylamine [88], tree-type multiple-head amine *bis*(amidoethyl-carbamoylethyl)octadecylamine [89]), and aromatic amines (4-hexadecylaniline [90], *bis*(2-(4-amino phenoxy)ethyl)ether (DAEE) [91]) were also investigated to prepare Au-NPs in aqueous and organic solutions. Interestingly, in the case of DAEE, the stabilization of Au-NPs was ensured by the polymer resulting from the oxidative polymerization of the diamine compound. For all the amines previously cited, Au-NPs with a narrow size distribution were characterized, except for *bis*

(amidoethyl-carbamoylethyl)octadecylamine which produced Au-NPs with a very broad size distribution (20 to 250 nm). 4-Aminothiophenol was also used as reducing and surface passivating agent for the preparation of organically capped gold nanoparticles [92]. The influence of the solvent in the reduction process was evidenced by the fact that the reduction only occurred in a mixture of high dielectric solvents such as *N,N*-dimethylformamide (DMF) and water, whereas no reduction was observed in water or in DMF. The morphology of the Au-NPs proved to be also strongly pH dependent. If no reduction was observed for pH above 12, highly acidic medium provided particles of different morphologies. Interestingly, nearly spherical Au-NPs of small size (3 nm) in a chain-like arrangement could be obtained under careful control of the reaction conditions. Small-sized nanoparticles (4.5 nm) were also characterized with dodecylaminomethanol as a reducer by electrospraying a gold precursor solution into the reductive solution of surfactant at room temperature [93]. In this novel and versatile approach, the reduction of Au(III) into Au(0) occurred upon oxidation of dodecylaminomethanol into dodecylaminomethanoic acid which subsequently decomposed into dodecylamine and formaldehyde. The main drawbacks of this method were the resulting broad size distribution of the spherical nanoparticles (5 to 20 nm) and the weak shape control obtained during the synthesis since other structures such as icosahedra, decahedra, and hexagons were additionally observed. It has to be noticed that when dodecylaminomethanol was previously employed as reducing and capping agent by the same authors using the conventional wet synthetic approach, Au-NPs of small size (3.9± 0.5 nm) were obtained, thereby showing the crucial role of the method employed in the size dispersity [94]. More surprisingly, Tween 80 or polysorbate 80, which is a nonionic surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid often used in foods, acted as reductant for a gold salt precursor in aqueous medium [95]. The control of the size of the particles was achieved by adjusting parameters such as the temperature or the concentration of both reagents. Tween 80 yielded extremely small-sized Au-NPs at 4°C even in the absence of light (1.48±0.02 nm) and a linear correlation between the temperature and the size could be clearly established. Further investigations concerning the reduction mechanism showed that the main factor determining the formation of Au-NPs was the presence of ethylene oxide units in the main chain. As previously postulated by Barnickel et al. [96], authors attributed the reductive ability of poly(ethylene oxide) to the formation of hydroperoxides with the oxygen for from the air, thus producing highly reductive species. The authors also discussed the potential contribution of the terminal OH groups of the poly(ethylene oxide) POE chain

in the reduction process. Such contribution of the OH groups in the reduction process was also investigated with β-D-glucose [97]. By simply adjusting the pH, β-D-glucose rapidly reduced Au(III) at ambient temperature under basic conditions. In addition to spherical Au-NPs, a few triangular particles were also observed. The authors clearly established the crucial role of the five hydroxyl groups in the complexation process of β-D-glucose to Au-NPs. The pH dependence of the reduction process was plausibly explained by generating highly reductive and electron-rich hydroxylates anions under basic conditions. The nanoparticles thus obtained displayed unusual and somewhat unexpected catalytic properties for the reduction of 4-nitrophenolate into 4-aminophenolate with the mild reductant NaBH$_4$. Honey, whose main ingredient is the monosaccharide fructose, was also investigated as an eco-friendly route to generate Au-NPs [98]. However, the presence of numerous other potential reducing agents such as vitamin C, glucose, sucrose, proteins, and enzymes did not allow to clearly determine the origin of the reduction process. Honey-mediated biosynthesis yielded mainly triangular nanoparticles mixed with spherical nanoparticles with a mean diameter of 15 nm. Notably, addition of a large excess of honey, compared with Au(III), inverted the ratio of nanotriangles and nanospheres. Recently, a fluorophore-substituted amine 1-pyrenemethylamine acted as a strong coating agent for Au-NPs following an auto-reduction pathway based on the electrostatic interaction of the amine with the gold salt followed by a reduction process promoted by the protonated amine [99]. The authors clearly showed that the shell around the metal core of the particles was composed of unpolymerized 1-pyrenemethylamines. Similarly, when luminol was used as reducing/capping agent, results indicated that residual luminol and the corresponding oxidation product 3-aminophthalate both coexisted on the surface of Au-NPs without any formation of polymer [100]. The size of the nanoparticles decreased while increasing the concentration of luminol and an extremely low stability of the colloidal solutions was observed for pH values under 3. Later, for a better understanding of the exact role of amines in the reduction process, an extensive study was performed on 14 amines [101].

Organic acids and salts

Due to the remarkable reducing capabilities of amines, amino acids and their derivatives were also studied for the synthesis of Au-NPs (see Fig. 6). Lauroyl glucose, lauroyl fructose, and lauroyl ascorbate formed spherical Au-NPs with sizes depending on the nature of the amino acid [102]. Lauroyl glucose and lauroyl fructose furnished spherical Au-NPs with core sizes ranging from 168 to 226 nm while smaller particles were obtained with lauroyl ascorbate (35 to 48 nm). Other amino acids such as tyrosine [103],
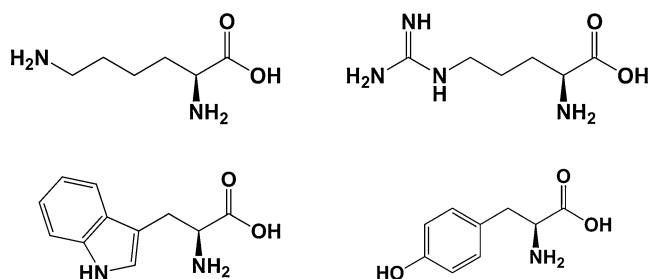
Fig. 6 Examples of amino acids commonly used for the synthesis of Au-NPs

alkylated tyrosine [104], aspartic acid [105], tryptophan [106], glutamic acid [107, 108], and tryptophan-containing peptide amphiphiles [109] were also identified as molecules able to reduce chloroaurate ions under mild experimental conditions in aqueous medium. Surprisingly, the shape of the particles formed with alkylated tyrosine dramatically changed when the spontaneous reduction occurred at the liquid–liquid interface or at the liquid–air interface. Very polydisperse nanospheres (5 to 100 nm) were obtained in the first case whereas nanoribbons and nanosheets were obtained in the second one. When tryptophan was used as reducing/capping agent, the resulting nanoparticles exhibited a polymer coating issued from intermolecular reactions between indole groups of the oxidized trypto-phans. In this study, polymerization of tryptophan was shown to occur through the secondary amine of the indole groups resulting in some degree to cross-linkage of the Au-NPs. In the case of glutamic acid, gold nanospheres obtained via a controlled HAuCl$_4$/glutamic acid molar ratio slowly formed nanochains by linear aggregation of the particles through an oriented attachment mechanism. This promising polymerization opens up the possibility to form, in a simple manner, numerous polymer-embedded nano-particles. Concomitantly, other authors carried out a comparative study with four amino acids, i.e., lysine, tyrosine, tryptophan, and arguinine [110]. When Au-NPs were prepared under similar conditions, the smallest particles were obtained with lysine (6±2 nm in diameter), the largest ones with tryptophan (60±5 nm in size) and intermediate size of particles with arguinine (10±5 nm). Surprisingly, examination of the particles obtained with tyrosine showed the presence of both spherical and rod-shaped particles. More recently, Au-NPs were also prepared with L-tyrosine, glycyl-L-tyrosine and L-arginine as peptides in alkali medium starting from potassium tetrabromoaurate as the precursor of gold [111]. If L-tyrosine and glycyl-L-tyrosine stabilized spherical particles with diameters com-prised between 5 and 40 nm, L-arginine stabilized particles of different morphologies. Interestingly, by mixing L-tyrosine and glycyl-L-tyrosine in the same reaction, and varying the ratio from 0% to 100%, Au-NPs with average

diameters ranging between those obtained for each individual peptide were obtained therefore providing a simple procedure to finely tune the size of the nanoparticles. Finally, a complete investigation on 20 different amino acids showed that tryptophan was the fastest reducing agent [112].

Weak organic acids have been also investigated. Inter-esting findings were notably obtained with tannic acid [113, 114], ascorbic acid [115], ascorbic-acid-based amphiphiles [116], gallic acid [117], 2-mercaptosuccinic acid [118, 119], lactic acid [120], cinnamic acid [121], and the synthetic antibiotic ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinylquinolone-3-carboxylic acid) [122]. The main interest of these weak organic acids compared with some other reducing agents relies on the fact that Au-NPs can be synthesized at neutral pH and at room temperature. The origin of the reducing ability of ciprofloxacin, which is in equilibrium with its zwitterionic form, results from an electronic transfer from the N–H group of piperazine to the gold salt, inducing the formation of Au(0). Another antibiotic, cephalexin which is a β-lactam antibiotic, also produced a robust coating for Au-NPs even if Au-NPs with a bimodal particle size distribution were obtained [123]. The coexistence of particles of 50–80 nm and larger particles (120–200 nm) was observed other structures than spheres were also characterized such as truncated triangles, hexa-gons, platelike, and other faceted particles. The study of the reduction process showed that the primary amine or the carboxylic groups present in the cephalexin do not partici-pate to the reduction and authors established the intracyclic sulfur atom to be responsible of it. In contrast, another antibiotic of similar structure, cefalor, which also possesses a primary amine and a carboxylic group, reduced the gold precursor via its primary amine [124]. The anchorage of the antibiotic via the primary amine retained the potent microbial activity of cefalor by maintaining the β-lactam ring available and the minimum inhibition concentrations was reduced to 10 μg mL^{-1}. Cefalor-capped Au-NPs were further immobi-lized onto poly(ethyleneimine) for biomedical applications. As a final example of biologically active molecules, dextran, which is used medicinally as an antithrombotic, produced well-monodispersed Au-NPs with a mean diameter of 13.6± 1.4 nm [125]. The resulting nanoparticles were further employed for the colorimetric detection of dihydralazine sulfate, a well-known vasodilator with antihypertensive properties, in urine samples. Carboxylate anions can also act as reducing/capping agents. Among all carboxylate anions, the most famous one is without contest citrate anion, involved in the well-known Turkevitch method [126]. This procedure, reported in 1951, is based on the use of trisodium citrate acting as reducing agent and as stabilizing agent by forming an electrically charged adsorption layer onto the surface of the nanoparticles. Further investigations of this method allowed the preparation of particles of predictable

sizes by varying the ratio between the reagents [127]. Turkevich stated, while examining the mechanism of the reduction process, the presence of an induction period preceding the nucleation and corresponding to the transformation of the citrate anions into a more reactive species, i.e., acetone dicarboxylate ions [128]. Subsequently to the formation of acetone dicarboxylate anions, a polymeric intermediate species forms between the gold salt and these anions which is then decomposed with nucleation of the particles when the polymer is large enough to stabilize the particles. More recently, the role of sodium citrate as a pH mediator in the growth of gold nanocrystals was studied and two distinct synthetic pathways were identified depending on the pH, i.e., one at low pH and one above pH=6.2–6.5 [129]. The first mechanism observed at low pH consists in three consecutive steps namely nucleation, random attachment, and intra-particles ripening (smoothing). The second mechanism taking place above pH=6.5 was determined to be related to the well-known nucleation-growth route. Close relationship between size, size–shape distribution, and evolution with the solution pH was clearly established. Following the Turkevich method few other sodium carboxylates have been investigated. Sodium alginate, which is a linear polysaccharide composed of β-D-mannuronic acid and α-L-guluronic acid, was recently studied [130]. In this particular case, Au-NPs with sizes ranging from 2 to 30 nm were obtained under UV photoactivation of this biopolymer used as stabilizing and reducing agent. A comparative study was performed with sodium acrylate and its corresponding poly(sodium acrylate) polymer. Interestingly, if the monomer produced Au-NPs with a narrow size distribution and a higher shape control with mainly spherical particles, the corresponding polymers produced Au-NPs with diameters ranging from 5 to 65 nm, depending on the molecular weight of the polymer [131]. Ionic liquids have also been studied. They constitute another particular class of salts exhibiting a melting point below 100°C. An ionic liquid based on purpurin-18 and choline was prepared for a possible future use in photodynamic therapy [132]. Reduction of HAuCl$_4$

by the choline-purine-18 photosensitizer produced mainly decahedra Au-NPs of 8–25 nm.

Liposomes

With the growing need of clean and nontoxic synthetic approaches, the focus also turned towards liposomes for the synthesis of spherical Au-NPs (see Fig. 7). The first article concerning the reduction of Au(III) by liposomes was reported in 1993 with egg yolk phosphatidylcholine as the phospholipid [133]. Ten years later, self-reduction of HAuCl$_4$ was also studied within onion-type multilamellar vesicles made of monoolein [134]. In this last case, Au-NPs polydisperse in size and shape were obtained and sphere-like and elongated particles were observed. The authors suggested that the reduction of Au(III) occurred via the oxidation of the terminal CH$_2$OH group of the monoolein into acid. Recently, Hernando et al. reported the spontaneous in situ synthesis of gold nanoparticles within ethosome bilayers, still based on phosphatidylcholine as the lipid [135]. Particles were almost spherical in shape and a better control of the nucleation process was obtained since particles ranged from 10 to 20 nm. The mean diameter of the lipid-based colloids decreased with increasing the temperature as a result of a faster nucleation kinetic. However, the amount of Au-NPs per vesicle was low (only two particles per ethosome) and the synthesis of Au-NPs at higher concentration of salt resulted in multipod clusters and bunches within the ethosomes. The authors rejected the probability of a self-reduction process within the ethosomes and they concluded that the reduction was carried out by water molecules with the phosphatidylcholine lipid acting as a catalyst.

Polymers

Polymers are undoubtedly among the most diversified organic-based reagents. The superiority of polymers, compared with small organic molecules, relies on the fact that these macromolecules can form a shell around the gold nanoparticles and can provide an excellent robustness against agglomeration in various extreme conditions (ba-


Fig. 7 Liposomes before and after encapsulation of Au-NPs
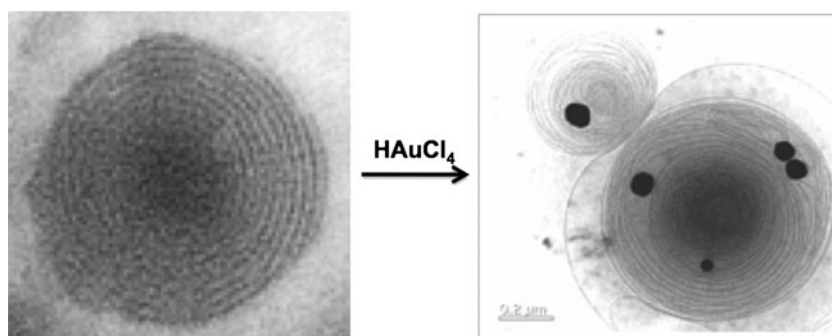
sicity, acidity, and elevated temperature). Additionally, there are several other interesting benefits emanating from the use of functional polymers such as the ability to self-assemble into nanostructures, therefore acting as structure-directing agents during crystal growth, or the possibility of polymers to induce an intra- and supramolecular organization of the metal colloid solution. A complete overview concerning the spontaneous generation of Au-NPs by polymers has been recently reported [136]. The first polymers studied were homopolymers such as poly(ethylene oxide) [137], diamine-terminated poly(ethylene oxide) [138], linear polyethyleneimine [139], amine-functionalized poly-(propylene imine)dendrimers [140], polydimethylsiloxane [141, 142], poly(vinyl pyrrolidone) [143–145], poly(allylamine) [146], poly(allylamine) hydrochloride [147], and recently polystyrene microspheres [148] (see Fig. 8). In this last case, the surface of the polystyrene microspheres were decorated with Au-NPs via a self-supported redox process attributed to the presence of reductive functional groups such as carboxylic or sulfate end-groups on the surface of the microspheres. Moreover, a careful size control of the crystal growth was assessed in terms of kinetics. The size of the spherical particles was precisely tailored by means of the reaction time or the concentration of the metal ions or both parameters. Nevertheless, an increase of the concentration of gold salt yielded additional anisotropic structures such as triangles and hexagons as a result of different growth rates of gold facets at high concentration. Homopolymers were not only used to reduce Au(III) and decorate their surface with Au-NPs but also to develop three-dimensional distributions of nanosized metal particles within the polymer. This strategy was successfully developed with polyaniline as a conjugated polymer that produced Au-NPs of 20 nm size upon conversion of the

polymer to a higher oxidative state [149]. Spontaneous reduction of Au(III) into Au(0) was also achieved with polyols such as glycerol upon microwave heating [150]. In these conditions, nanoprisms of 7.1 ± 0.2 nm were obtained in addition to spherical nanoparticles with an average size of 6.9 ± 0.1 nm. Alkylated polyethylenimines promoted the formation of nonspherical Au-NPs and nanoplates were selectively formed [151]. The first block copolymer initiating the nucleation of Au-NPs was reported in 2004 under the form of a triblock copolymer namely poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-b-PPO-b-PEO) [152, 153]. The amphiphilic copolymer proved to be very efficient in stabilizing the colloidal dispersion in water and the size and the shape of the resulting particles were controlled by means of the molecular weight of the triblock copolymer as well as the length of each block. Au-NPs synthesized with the copolymers were stable for 8 months whereas aggregation of Au-NPs was observed after only 2 days with the corresponding POE homopolymer. A series of six diblock copolymers with various functional groups were also studied [154]. The self-reduction of Au(III) by double hydrophilic block copolymers proceeded slowly depending on the characteristics of the copolymers. Spherical nanoparticles were selectively obtained only with poly(ethylene glycol)-block-poly(ethylene imine)-poly(acetic acid) (PEG-b-PEIPA) with an average size of 25 nm. Other block copolymers such as R-biotinyl-poly(ethyleneglycol)-block-[poly(2-(N,N-dimethylamino)ethyl methacrylate)] [155] or linear-dendritic copolymers containing hyperbranched poly (citric acid) and linear poly(ethylene glycol) blocks (PCA–PEG–PCA) [156] were also studied. Interestingly, HAuCl₄ can also be used as initiator of polymerization and this strategy was successfully developed with o-phenylenedi-

Fig. 8 Examples of polymers with dual function of reducing and capping agents: **a** poly(vinyl pyrrolidone), **b** poly(ethylene oxide), **c** polyethyleneimine, and **d** amine-functionalized poly-(propylene imine)dendrimers
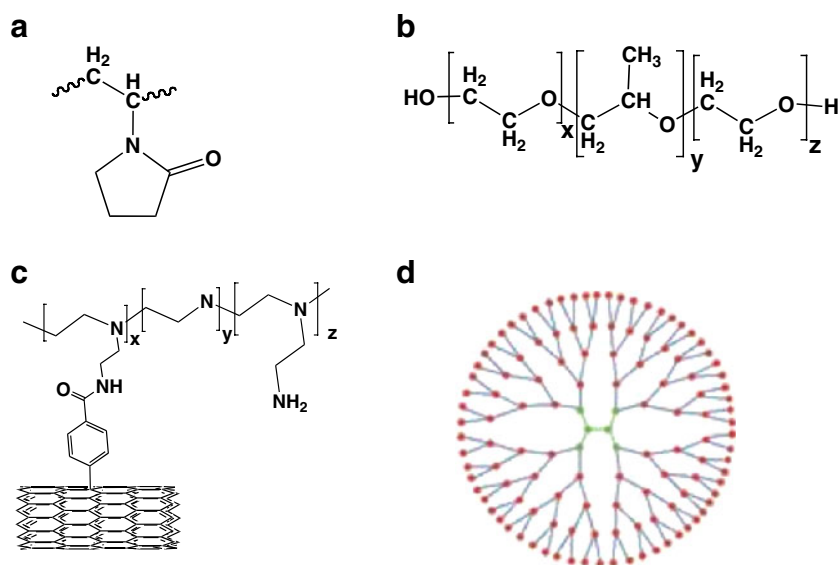
amine as the monomer to produce the conducting polymer poly(*o*-phenylenediamine) [157]. The advantage of this strategy is that Au-NPs are well-dispersed and homogeneously encapsulated within the polymer matrix. Previously and unexpectedly, the synthesis of poly(*o*-phenylenediamine) in similar conditions resulted in a completely different result since a phase separation between the polymer and the metal particles was clearly observed [158]. Recently, nanospheres of poly(*o*-phenylenediamine) successfully initiated the reduction of Au(III) and served as support for the resulting nanoparticles [159]. Study of the catalytic performances of poly (*o*-phenylenediamine) submicrosphere-supported Au-NPs showed a high selectivity for the oxidation of benzyl alcohol in benzaldehyde. Selectivity as high as 97:3 (benzaldehyde/benzoic acid) was determined for the oxidation of benzyl alcohol under aerobic conditions. In a similar approach, the synthesis of polyaniline from aniline using auric acid as the oxidizing agent produced Au-NPs whose position strongly depended on the reaction conditions. Polyaniline nanofibers [160] or nanoballs [161] decorated with Au-NPs were reported while Au-NPs stabilized within the polymer [162] were also characterized. Several other aniline derivatives were also tested and oxidative polymerization was also reported with *o*-anisidine [163] and *o*-aminophenol [164]. To circumvent the need of an external reducing agent, polymers were also used for the decoration of various nanostructures such as single-walled carbon nanotubes (SWNTs) [165], polypyrrole nanotubes [166], and PEGylated nanogels [167]. Sufficient solubility was achieved upon covalent functionalization of SWNTs with polyethyleneimine and functionalized SWNTs could reduce $HAuCl_4$ in water. Discrete nearly spherical Au-NPs were detected within the polymer and Au-NPs with mean diameters ranging from 50 to 500 nm could be prepared in a controlled manner by adjusting the reaction time. Similarly, Au-NPs with controllable size were obtained with polypyrrole nanotubes. Particles with the narrowest average size distribution (6 nm) were obtained with PEGylated nanogels acting as nanoreactors. If particles of small size were obtained, a limited number of bigger particles per nanogel were also observed (ten particles/nanogel). Biopolymers such as sodium alginate [130] or gum Arabic [168], which is a natural and harmless polysaccharide derived from acacia trees, proved to be cost-effective and reproducible alternatives to the chemical synthesis by producing Au-NPs of high stability over the time. Gellan gum, which is a linear anionic heteropolysaccharide widely used in food as gelling agent, also produced highly stable Au-NPs [169]. Carbohydrate-capped Au-NPs were further used to load a well-known anticancer, i.e., doxorubicin hydrochloride. When used as carriers for drug delivery, enhanced cytotoxic effects on human glioma cell lines LN-18 and LN-229 were

evidenced for the cationic anthracycline drug. Recently, the surface of Gellan gum reduced gold nanoparticles was functionalized by other anticancer agents namely sophorolipids which are a class of glycolipids [170]. The cytotoxicity effect of sophorolipids-functionalized Au-NPs was studied on human glioma cell line LN-229 and human glioma stem cell line HNGC-2. The most appealing result was obtained when a synergetic effect was obtained while loading the former Au-NPs with doxorubicin hydrochloride thus producing doxorubicin-capped sophorolipids-functionalized Au-NPs. This result represents one of the first examples of combination therapy using Au-NPs for the eradication of glioma cancer cells and glioma stem cells. Prior to this study, the direct coating of Au-NPs and Ag-NPs by sophorolipids had been developed by the same authors and the cytotoxicity of the resulting nanoparticles evaluated [171]. The study of the cytotoxicity of the functionalized Au-NPs on human hepatocellular cell lines showed a higher cytocompatibility of Au-NPs compared with Ag-NPs.

Metal complexes and inorganic systems

Recent researches have also concerned a limited number of inorganic systems acting as reducing and stabilizing agent. Notably, carbon nanofibers and silica nanotubes were decorated by Au-NPs of small size [172]. Reduction of the noble-metal salt by carbon nanofibers was attributed to the strongly reductive functional groups on the outside surface. Interestingly, no Au-NPs were found in the solution, illustrating that the reduction process was only occurring inside the nanofibers even if TEM analyses later proved that Au-NPs were localized in the interior and at the surface of the nanofibers. This strategy enabled, in a second step, to fill silica nanotubes with Au-NPs by forming the nanotubes around the carbon nanofibers used as a template. In the final step, pyrolysis at 550°C removed the carbon nanofibers, thus leading to pure silica nanotubes embedded with noble-metal nanoparticles. C_{60} dianion was also used to reduce tetrachloroauric acid [173]. Contrarily to neutral C_{60}, C_{60}^{2-} is an electron-rich species that displays a strong reducing ability toward numerous organic functional groups ($N-N^+$, $C = C-EWG$ (where EWG is electron withdrawing groups) and $C = O$ bonds) [174]. When opposed to a gold salt, spontaneous reduction occurred and Au-NPs with a mean diameter of 17 nm were obtained. The presence of aggregates is also observed with an average size of 100 nm resulting from the strong carbon-carbon interactions. Finally, the strong affinity of C_{60} molecules for gold metal and the tendency of fullerenes to self-aggregate ensured that every gold nanospheres were loaded with fullerenes. To date, only two metal complexes were reported to reduce $HAuCl_4$ and to stabilize Au-NPs thus formed [175]. The
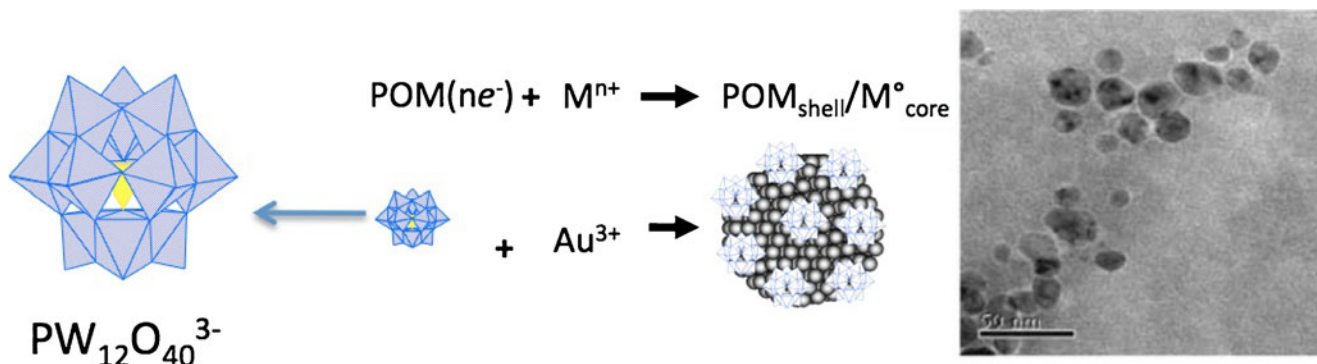
Fig. 9 TEM image of Au-NPs stabilized by polyoxometalate $PW_{12}O_{40}^{3-}$

first example, a Fe(III)-citrate complex was designed to develop a photochemical version of the Turkevich method. However, in this study, citrate anions did not efficiently absorb the visible light, therefore rendering the photoactivation process inefficient. In the presence of ferric ions, Fe(III)-citrate complexes with a high molar absorptivity in the visible region are formed, enabling the photoactivation pathway to proceed. Carbon-centered radicals are generated from the visible-light photolysis of Fe(III)-citrate complexes, thus producing highly reductive species. This reaction, based on a reduction process mediated by iron(III) ions, elegantly ensured the formation of Au-NPs and citrate anions provided a robust shielding against agglomeration. We recently reported the first iridium(III) complex exhibiting the dual function of reducing and capping agent for the design of small-sized Au-NPs at room temperature without any external activation [176]. In this example, the reduction process involved the dithiolate appended iridium(III) complex in basic medium and resulted from a cascade mechanism namely oxidation of the ligand, reduction of the gold salt, stabilization and functionalization of the Au-NPs. This first example of functionalization of Au-NPs by a polypyridyl Ir(III) complex produced Au-NPs with an extremely tight distribution (3–4 nm). Recently, ammonia

borane complex (or borazane), which is one of the simplest complexes based on Lewis acid–base interactions, was reported to stabilize Au-NPs after being transformed into a BNHx polymer [177]. The originality of that specific approach relied on the fact that the ammonia borane complex also acted as the solvent of the reaction, therefore justifying the terms of atom-economy green route employed by the authors. Au-NPs were synthesized using $AuCl_3$ as the starting metal precursor and particles with of 6 to 11 nm in diameter were obtained. Polyoxometalates (POMs) that are well-defined molecular metaloxygen anions constitute another promising class of inorganic reagents for the synthesis of Au-NPs. POMs have the unique ability to implement stepwise redox reactions while keeping their structure mainly unchanged. Once reduced, POMs such as $[SiW_{12}O_{40}]^{4-}$ [178] and $H_3PW_{12}O_{40}$ [179] efficiently transfer electrons to Au(III) therefore producing Au-NPs (see Fig. 9). Interestingly, the shape of the resulting particles was shown to be highly dependent on the nature of the POM and on the nature of the metal precursor. The use of $[SiW_{12}O_{40}]^{4-}$ and a gold salt formed, after reduction, spherical Au-NPs whereas the use of vanadium containing POMs with a silver salt produced nano and micro-ribbons and saws mixed with a
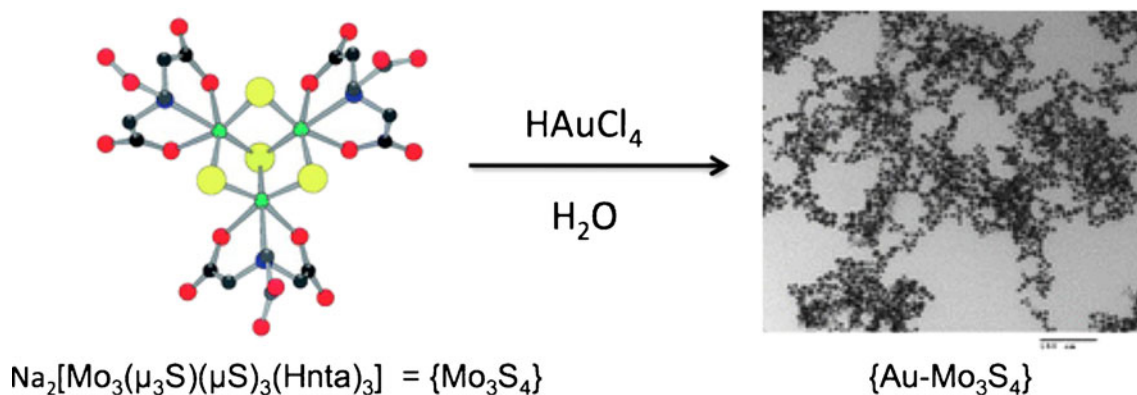

Fig. 10 TEM image of Au-NPs stabilized by polyoxothiometalate $Na_2[Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3(Hnta)_3]$

few discrete spherical Ag-NPs [180]. Similarly, high built-in capability of $Na_2[Mo_3(\mu_3\text{-}S)(\mu\text{-}S)_3(Hnta)_3]$ (Hnta being the nitrilotriacetate ligand) was also shown for this oxothio-metallate in water at room temperature (see Fig. 10). Particles with an average diameter size of 9.5 ± 0.5 nm were characterized [181].

Conclusions

A careful survey of the literature concerning all agents exerting the dual function of reducing agent for gold salts and stabilizing agent for Au-NPs clearly shows the predominance of the nature in this field, at least in terms of number of papers. However, this approach often provides polydisperse and poorly characterized Au-NPs made with unreliable and variable materials. This approach is also not necessarily a guarantee of Green chemistry or biocompatibility as molecules present during the synthesis might prove to be toxic to humans. Concerning the chemical approach, apart from all the acids, carboxylates and polymers widely investigated, few other reagents are available and it can be surprising that, to date, only two metal complexes have shown the ability to both reduce Au (III) and stabilize and functionalize the Au-NPs thus formed. However, these reducer-free approaches elegantly ensure the formation of Au-NPs, usually free of byproducts. Additionally, there is still a real improvement needed for these single-reagent methods in order to reach a higher degree of control in the size and shape of the Au-NPs considering the growing demand of well-defined Au-NPs, for instance in electronics and biology.

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