

Chapter 2

Noble Metal Nanoparticles

Abstract To synthesize noble metal nanomaterials in controlled sizes and dimensions, various approaches and mechanisms have been developed. The successful utilization of noble metal nanoparticles (NMNPs) relies on the availability of synthetic methods generating nanoparticles with the desired characteristics, namely high solubility in water, adequate morphology, and surface functionalities. Control over the shape and size of the nanoparticles is usually achieved through the careful selection of the experimental conditions, namely reducing agents, type and concentration of precursors, reaction time, temperature, UV light, (co)solvent, and capping agents. Depending on the reduction potentials of the metal precursor and the reducing-agent systems, reduction can occur at room temperature or at elevated temperatures. In general, citrate plays a role as a stabilizing agent with preparations of gold nanoparticles requiring relatively high temperatures due to its weak reducing strength. The use of amine–borane complexes is essential for the syntheses of monodisperse metallic nanoparticles. Upon the addition of strong reductants, such as NaBH_4 , metal cations are reduced rapidly, resulting in an immediate color change of the reaction mixture. Rationally designed molecular building blocks allow for the precise control of particle size and morphology of the supramolecular aggregate, and various defined structures, including spherical micelles, rodlike micelles, or vesicles. Molecules which control the overall crystal growth are known as “capping agents,” the term frequently used for specific adsorption of surface-active molecules on selective crystal planes of a particular geometry. Additives such as surfactants, polymers, foreign ions, ligands, and impurities present in the reaction medium have been observed to play important roles in controlling the morphology of particles produced. Surfactants, ligands, or polymers were commonly added as stabilizers to impart stability to nanoparticles against aggregation, since colloidal particles tend to aggregate to decrease the overall surface area and energy. In a typical liquid-phase synthesis, the nanoparticle formation process undergoes three distinct stages as follows: (1) reduction and generation of active nuclei; (2) formation of seed particles upon collision of active nuclei; and (3) formation of larger nanoparticles via a growth process, which may be Ostwald ripening or aggregation. The nanoparticle growth is generally categorized by two processes: diffusion-controlled Ostwald-ripening and

aggregation/coalescence. Nowadays, a molecule which can act both as a reducing and capping agent is preferred so that the reaction takes place in one step and there is no need for an external reducing agent. Multifunctional amines and nitrogen-containing polymers have also been tested for the synthesis of nanoparticles. Poly(ethylene oxide)-poly(propylene oxide)-based block copolymers are well known as dispersion stabilizers and templates for the synthesis of mesoporous materials and nanoparticles. Coordination chemistry offers simplicity, stable bonding, and ligand-metal specificity, enabling ligand-bearing components to be assembled into supramolecular structures using appropriate metal ions. This approach is particularly compatible with surface chemistry, as binding of metal ions activates the surface toward ligand binding, and vice versa. Some stabilizing agents can also be used as a reducing agent. Ionic liquids (ILs) are a viable option as stabilizing agents because of their ionic character and can be easily made task-specific as phase-transfer catalysts due to their tunable nature. Ligand exchange reactions have proven a particularly powerful approach to incorporate functionality in the ligand shell of thiol-stabilized nanoparticles and are widely used to produce organic- and water-soluble nanoparticles with various core sizes and functional groups. NMNPs can be intercalated into the gallery regions of montmorillonite and formed hybrid framework. Models of particle (crystal) development consider two basic steps: nucleation and growth. The creation of a new phase from a metastable state is nucleation. Seed-mediated growth method has been demonstrated to be a powerful synthetic route to generate a range of different types of metal nanoparticles. This method separates the nucleation and growth stage of nanoparticle syntheses by introducing presynthesized small seed particles into a growth solution typically containing a metal precursor, reducing agent, surfactants, and some additives. Dissolution of silver nanoparticles, for example, occurs through oxidation of metallic Ag and release of Ag^+ into solution (or dissolution rate is accelerated). Release of Ag^+ is determined by intrinsic physicochemical properties of silver nanoparticles and by those of the solution. Parameters that either enhance or suppress silver nanoparticle dissolution are ionic strength, pH, dissolved oxygen concentration, temperature, dissolved complexing ligands (organic matter, sulfur, chlorine), silver surface coating, shape, and size. The surfactants find their way to various environmental segments and thus pose serious health hazards. Several different polymer-based anticancer agents have been approved for clinical use, for passive tumor targeting. Prominent examples of macromolecular drug carrier systems evaluated in patients are poly(ethylene glycol), poly(L-glutamic acid), poly[N-(2-hydroxypropyl)methacrylamide], and their copolymers. Copolymers based on N-(2-hydroxypropyl)methacrylamide (i.e., HPMA) were used to improve the tumor-directed delivery of doxorubicin.

Keywords Noble metal nanoparticles • Reductants • Surfactants • Capping agents • Ligands • (Co)polymers • Particle nucleation and growth • Dissolution • Ionic liquids and biohybrids

Abbreviations

3D	Three-dimensional
AA	Ascorbic acid
AFM	Atomic force microscopy
AgNPs	Silver nanoparticles
AuNPs	Gold nanoparticles
AuNRs	Gold nanorods
BDAC	Benzyltrimethylhexadecylammonium chloride
[BMIM][BF ₄]	1-butyl-3-methylimidazolium tetrafluoroborate
BSA	Bovine serum albumin
CHIT	Chitosan
CMC	Critical micellar concentration
CMT	Critical micellar temperature
CTAB	Cetyltrimethylammonium bromide
CTAC	Cetyltrimethylammonium chloride
DMEM	Dulbecco's minimum media
DMF	<i>N,N</i> -dimethylformamide
DNA	Deoxyribonucleic acid
DSC	Differential scanning calorimetry
fcc	Face-centered cubic
FDTD	Finite-difference time domain
F-faces	Flat faces
FTIR	Fourier transform infrared spectroscopy
GCE	Glassy carbon electrode
GFLG	Glycylphenylalanylleucylglycine
GO	Graphene oxide
GSH	Glutathione
HAADF	High-angle annular dark field
HCPA	Hexachloroplatinic acid
HPMA	<i>N</i> -(2-hydroxypropyl)methacrylamide
HRTEM	High-resolution TEM
HSA	Human serum albumin
HTAB	Hexadecyltrimethylammonium bromide
ILs	Ionic liquids
K-faces	Kinked faces
LB	Langmuir–Blodgett
LbL	Layer-by-layer
LCST	Lower critical solution temperature
LED	Light-emitting diode
LMWT	Low molecular weight thiol
LSPR	Localized surface plasmon resonance
MC@AgNPs	Silver nanoparticle-decorated microcapsules
MC@AuNPs	Gold nanoparticle-decorated microcapsules
MC@PtNPs	Platinum nanoparticle-decorated microcapsules

MCs	Microcapsules
MES	2-(<i>N</i> -morpholino)ethanesulfonic acid
MIES	Metastable impact electron spectroscopy techniques
MMT	Montmorillonite
MNPs	Metal nanoparticles
NaBH ₄	Sodium borohydride
NaPA	Sodium polyacrylate
NaOC ₂ H ₅	Sodium ethoxide
NMNPs	Noble metal nanoparticles
NMs	Nanomaterials
NPs	Nanoparticles
NRs	Nanorods
o/w	Oil-in-water
PA	Polyacrylate
PAM	Polyacrylamide
PAN	Polyacrylonitrile
PBS	Phosphate buffer saline
PCS	Photon correlation spectroscopy
PDPAEMA	Poly2-(diisopropylamino) ethyl methacrylate
PEG-SH	Thiol-PEG
PEO	Poly(ethylene oxide)
PEO- <i>b</i> -PDHPMA- <i>b</i> -PDPAEMA	(poly(ethyleneoxide)- <i>b</i> -poly(2,3-dihydroxypropyl methacrylate)- <i>b</i> -poly[2-(diisopropylamino) ethyl methacrylate])
PIC	Polyion complex
PI	Pullulan
pNIPAM	Poly(<i>N</i> -isopropylacrylamide)
POSS	Polyhedral oligomeric silsesquioxane
PPDO	(poly(<i>p</i> -dioxanone))
PPO	Poly(propylene oxide)
PtNPs	Platinum nanoparticles
PTPS	Amphiphilic polyhedral oligomeric silsesquioxane-containing thiol groups
PVA	Poly(vinyl alcohol)
PVP	Polyvinylpyridine
PVPo	Polyvinylpyrrolidone, poly(<i>N</i> -vinyl-2-pyrrolidone)
SERS	Surface-enhanced Raman scattering
S-faces	Stepped faces
sMNPs	Spherical metal nanoparticles
SPB	Surface plasmon band
SPEEK	Sulfonated poly(ether-ether) keton
SPL	Scanning probe lithography

SPR	Surface plasmon resonance
STM	Scanning tunneling microscopy
TEM	Transmission electron microscope
TGA	Thermal gravimetric analysis
TMPTA	Trimethylolpropane triacrylate
rtTEM	Real-time TEM
UPD	Underpotential deposition
UPS	Ultraviolet photoelectron spectroscopy
UV	Ultraviolet
VOCs	Volatile organic chemicals
XANES	X-ray absorption near-edge spectroscopy
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction
γ	Surface energy

2.1 Introduction

The rapid development of nanotechnology worldwide is accompanied by massive generation and usage of engineered nanomaterials (NMs) or nanoparticles (NPs) even though the potential nanostructure impacts of these materials are largely unknown. The interest in nanomaterials is a result of the extreme dependence of properties (electronic, magnetic, optical, mechanical, etc.) on particle size and shape in the 1–100-nm regime. These interesting new properties at the nanoscale are the basis of the nanomaterial's various applications. Reducing a material's size to the nanometer length scale (which is the length scale of the electronic motion that determines the material's properties) makes it sensitive to further reduction in size or a change in shape. The molecular design of functional materials at nanoscale supports innovation expected to revolutionize present technology and overcome societal challenges including sustainable energy supply, information storage, and the advancement of medical treatments. Research involving the use of different types and designs of nanomaterials continues to evolve with the growth of nanotechnology for in vivo applications in such fields as drug delivery, medical imaging, diagnostics, and engineering technology.

Noble metal nanoparticles (NMNPs) can be prepared by both “top-down” and “bottom-up” approaches. For “top-down” procedures, a bulk state metal is systematically broken down to generate metal nanoparticles of desired dimensions. In this case, particle assembly and formation is controlled by a pattern or matrix. However, the “top-down” method is limited concerning the control of the size and shape of particles as well as further functionalization [1]. In contrast, in the “bottom-up” strategy, the formation of nanoparticles originates from individual molecules (atoms), because it involves a chemical or biological reduction [2]. Classical

procedure for nanoparticle synthesis is based on the chemical reduction of metal salts with sodium citrate (Turkevich method) and requires high temperature. Biological reduction is considered a green approach and leads to stable nanoparticle, but they are not uniform and are synthesized fairly slowly. A number of techniques have been used for producing metal nanoparticles, including vapor-phase techniques [3], sol-gel methods [4], sputtering [5], coprecipitation [6], chemical reduction [7], sonochemical reduction [8], laser ablation [9], annealing from high-temperature solutions [10], metal evaporation [11], Ar^+ ion sputtering [12], sonoelectrochemical reduction [13], and solvothermal and surfactant-templated solvothermal reactions. Furthermore, two main colloidal methods are broadly employed for the preparation of NMNPs: (co or nano)precipitation and chemical reduction. In some cases, the presence of surfactant (capping agent) is required to control the particle nucleation, growth, and stability. Typically, the coprecipitation reactions involve the thermal decomposition of organometallic precursors and the precipitation of new reaction materials or compounds [14]. The chemical reduction occurring in colloidal assemblies is another approach for the formation of size- and shape-controlled nanoparticles [15]. A major benefit of chemical methods is their relatively inexpensive investment of capital equipment. Gold and silver nanocolloids have also been synthesized using a variety of above-mentioned methods, including chemical and bioreduction and synthesis in micellar solutions [16, 17]. The chemical reduction method involves two steps: nucleation and successive growth. When the nucleation and successive growth are completed in the same process, it is called *in situ* synthesis; otherwise, it is called the seed-growth method.

The successful utilization of NMNPs (e.g., silver or gold nanoparticles, AgNPs, or AuNPs) in biological assays relies on the availability of synthetic methods generating nanoparticles with the desired characteristics, namely high solubility in water, adequate morphology, size dispersion, and surface functionalities. Most commonly, NMNPs are synthesized by chemical or electrochemical reduction of noble metal precursor compounds (e.g., Au(III) and Ag(I) salts) in the presence of a capping agent, i.e., a compound able to bind to the nanoparticle surface blocking its growth beyond the nanometer range and stabilizing the colloid in the particular solvent used. Control over the shape and size of the NPs is usually achieved through the careful selection of the experimental conditions, namely reducing agent, reaction time, temperature, UV light (co)solvent, and capping agent. A common approach is to use capping agents with weak or strong affinities or both for noble metals. This mostly allows the synthesis of gold nanoparticles with good size dispersion but usually only soluble in organic solvents [18] requiring an additional step of extraction of the particles into water. In addition, exchange of strongly binding capping agents is usually cumbersome, which makes this type of gold nanoparticle less versatile for biological applications. Due to its simplicity and high yield, the most commonly used method for preparation of spherical AuNPs for biological assays is the citrate reduction method [19]. The use of citrate as a capping agent is very convenient due to its easy postsynthesis treatment, since it can be

easily replaced by other capping agents, e.g., thiol capping agents, bearing an appropriate functionality for binding of the biological analyte of interest.

NMNPs play important roles in different branches of science [20], such as chemical catalysis, catalysts for the growth of nanowires, nanomedicines, nano-electronics. For most of those applications, their size and size distribution control are of key importance. Furthermore, composite and alloy nanoparticles exhibit unique electronic, optical, and catalytic properties that are different from those of the corresponding individual metal particles [21]. Research into NMNPs is a very active field in both fundamental scientific studies and applications—nanoscale materials [22]. A number of groups have been involved in synthesizing metal nanoparticles of different shapes, such as spheres [23], rods [24], triangular-shaped particles [25], prisms [26], nanowires [27], tripods, and tetrapods [28], using both chemical synthesis and lithography techniques, while other groups have investigated the optical [29] and electronic [30] properties of metal nanoparticles. The combination of these fields of research may lead to applications, such as optical data storage devices [31], biosensors [32], and new catalysts [33]. These applications are based on combining two principles: (1) surface functionalization for providing the colloidal stability and biocompatibility of particles, the molecular recognition of conjugates, etc., and (2) the excitation of plasmon resonances in the visible or near-IR region in order to obtain unique optical properties.

It is now well understood that the shape of the nanoparticles plays an important role in modulating their electronic and optical properties and, consequently, synthesis procedures that yield different shapes such as nanodisks [34], nanorods [35], nanowires [27], cubes [36], triangles [25], frames [37], and shells [38] are receiving considerable attention. The exciting electronic and optical properties displayed by metal nanoparticles [39] has resulted in their exploitation in a number of applications that include single-electron tunneling devices [40], nonlinear optical devices [41], electron microscopy markers [42], and the emerging area of plasmonics [43]. Some NMNPs are being studied in detail and are known to be excellent substrates for surface-enhanced Raman scattering (SERS) to probe single molecules [44].

Colloids of gold nanoparticles are one of the most stable and easiest to manipulate. However, preparing monodisperse gold nanoparticles is still not easily accomplished on a useful synthetic scale, especially if the stabilizing ligand of these particles is changed from the often used alkylthiols. The general synthetic procedure to prepare nearly monodisperse gold colloids involves the reduction of metal salts in the presence of surfactants and then stabilizing the particles with a capping ligand present in the solution [18]. In general, particle size and size distribution play a significant role in controlling the properties of any colloid based upon a nanomaterial [45, 46]. As a result, many groups have developed a variety of approaches to achieve particle separation and to narrow the size distribution of particles in a colloidal solution. Unlike molecular systems, it is often difficult to employ crystallization for colloidal structures, and the methods that have been used successfully are performed primarily in organic media. In such media, precipitation methods have been developed and used with great success for certain compositions [47]. Such methods, however, require an empirical tuning of the experimental conditions

to effect optimum size-selective precipitation or crystallization. The size distribution is further narrowed by size-selective precipitation [48]. Some authors demonstrated the advantage of a “digestive-ripening” procedure to prepare monodisperse colloids directly, avoiding the size-selective precipitation [49]. Other postsynthetic methods for refining particle size or separating a mixture of particles of different sizes in organic media include digestive ripening [50], use of supercritical fluids [51], gas pressurization [52], high-performance liquid chromatography [53], and size-exclusion chromatography [54]. In contrast, the improvement of the particle size distribution in aqueous media has been a more challenging task and is usually performed by filtration [55] or chromatographic methods such as size-exclusion chromatography [56] and capillary electrophoresis [57]. Such techniques, however, are somewhat limited in throughput and the types of compositions that can be used due to different degrees of interactions with column supports or filtration membranes and the need for specialized equipment (see more in the previous chapter). For particles dispersed in aqueous media, it would be a major advance if one could utilize the inherent chemical recognition properties of biomolecules [58–60] to size-selectively assemble particles.

Fendler and coworkers demonstrated that surface-modified hydrophobic colloidal nanoparticles may also be organized at the air–water interface—more specifically, on the surface of water—and that multilayer films of the nanoparticles could be formed on suitable substrates by the Langmuir–Blodgett (LB) technique [61]. A number of other groups have now used this method to form multilayer films of gold particles [62], polymer-capped platinum colloidal particles [63], buckyballs [64]. The Brust synthesis procedure [18] wherein gold nanoparticles are synthesized and capped with alkanethiols in a nonpolar organic phase continues to be the most popular means of obtaining hydrophobic gold nanoparticles that are readily dispersible in different nonpolar/weakly polar organic solvents [65, 66]. It was demonstrated an alternative method for obtaining hydrophobic gold nanoparticles synthesized in water by electrostatic coupling with fatty amine molecules present in nonpolar organic solvents [67]. The alkylamine-stabilized colloidal gold particles could be separated out in the form of a powder and dissolved in different organic solvents [67].

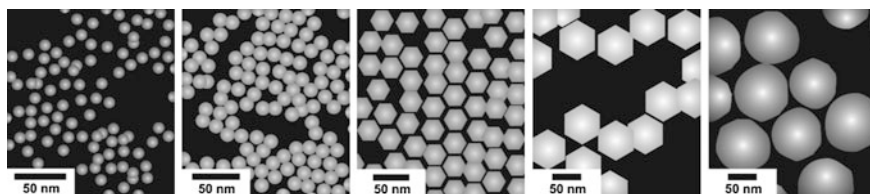
Spherical noble metal nanoparticles (sNMNPs) (gold, silver, $\text{SiO}_2\text{@Au}$ or Au@SiO_2 core@shell, etc.) have been the primary choice of colorimetric probes and nanocomposites. Numerous assays have been developed for a wide range of analytes (e.g., DNA, protein, metal ions, enzyme, and small molecular drugs) [68]. These assays exploit interparticle cross-linking and noncross-linking aggregation mechanisms that usually involve receptor-conjugated sNMNPs and unmodified sNMNPs, respectively. Compared to the extensive research with the spherical nanoparticles, the use of nonspherical particles with anisotropic configuration to construct plasmon coupling-based colorimetric assays has been less well demonstrated, except for a few examples using gold nanorods (AuNRs) [69, 70]. The traditional *in situ* synthesis provides spherical or quasispherical NMNPs. The disadvantage is, however, that when the size increases, it becomes out of control, and the shape is not controlled either. Therefore, the seed-growth strategy has emerged

as a very efficient method to synthesize monodispersed AuNPs with large sizes (up to 300 nm) precisely and with well-defined shapes [71, 72].

In the course of the seed-growth synthesis of NMNPs, the formation of seeds takes a significant place correlated to the size, shape, and surface properties that are controlled by the amount and nature of reducing agent and stabilizer, and their ratio to the metal precursor. The earliest gold nanoseeds were proposed by Natan [73] using citrate reductant and capped spherical gold nanoseeds for the overgrowth of spherical AuNPs. Murphy's group [74, 75] reported the synthesis of 3.5-nm citrate-capped gold seeds by dropping an ice-cold aqueous solution of NaBH_4 into a solution of a mixture of HAuCl_4 and citrate. These seeds were originally used for the formation of AuNRs. This procedure of gold seed formation was modified by El-Sayed [76] using hexadecyltrimethylammonium bromide (HTAB) as the stabilizer instead of citrate. These gold seeds with a diameter smaller than 4 nm were used to promote the narrow dispersity of AuNRs. Subsequently, this seed formation was regarded as the most primary nucleation process in the synthesis of AuNPs. Other monodispersed, large-sized, spherical, or quasispherical AuNPs, AuNRs, and other shaped AuNPs have been synthesized using the seed-growth method.

Natan and coworkers [73, 77] prepared gold nanoparticles between 20 and 100 nm by adding citrate-capped, NaBH_4 -reduced seeds into a "growth" solution containing a mild reducing agent such as citrate [77, 78] or hydroxylamine [79]. These results provided an improvement of physical properties compared with the Turkevich and Frens method. However, this synthetic route also generated a small population of rod-shaped AuNPs as impurities. Later, Murphy's group [80] improved the method by using ascorbic acid as a reducing agent as mild as citrate in growth solution and using cetyltrimethylammonium bromide (CTAB) as a stabilizer to synthesize monodispersed spherical AuNPs up to 40 nm (the citrate-stabilized AuNPs with a relative standard deviation that was lower than 10% were considered as monodisperse) [80, 81]. This method was later used by Han's group for the synthesis of icosahedral AuNPs having controlled size (from 10 to 90 nm) (Scheme 2.1) [82].

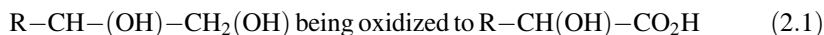
Later, Liz-Marzan's group first reported the synthesis of gold nanoparticles via the seed-growth method up to 200 nm, also showing optical properties with quadrupolar modes [79]. Highly monodispersed, spherical, citrate-stabilized AuNPs were synthesized up to 300 nm by using hydroquinone [71] or ascorbic acid [84] as



Scheme 2.1 TEM-like images of AuNPs (diameter) in solution (*from a left side*) ~ 11.0 , ~ 13.3 , ~ 32.2 , ~ 69.0 nm, and (*to the right side*) 87.3 nm [82, 83]

reducing agent in the seed-growth process. Reaction conditions such as temperature [72], pH [72], gold precursors to seed particle concentration [72] and citrate concentration [81] were considered to affect the size distribution and shape of the AuNPs.

The formation of gold clusters by chemical reduction of $\text{HAu}^{\text{III}}\text{Cl}_4$ has been well described by Gachard et al. [85]. The gold salt reduction may occur either by UV irradiation or by chemical reduction. To evaluate the effect of light on gold reduction, the synthesis was performed in the dark, and gold nanoparticles were generated, which ruled out light as a reducing agent. Regev et al. [86] have proposed that the lipid monoolein, the onion supplier of OH groups, acts as a reductant for the gold salt:



when Au(III) ions are reduced to Au(0). On the other hand, it was proposed that ethanol as well as water can act as very weak reducer agents [87].

A number of reports are available in the literature for the synthesis of silver nanoparticles by the chemical reduction of silver ions by sodium citrate or sodium borohydride [88], reduction in reverse micelles [89], biological methods [90, 91], electrochemical methods [92], photochemical methods [93], radiation methods [94], laser ablation [95], solvent reduction in the presence of surfactants [96], sonochemical methods [97], and reduction at two-phase liquid-liquid interfaces [98]. The unique size- and shape-dependent optical [99, 100] and antimicrobial [101, 102] properties of silver nanoparticles have prompted increasing interest of chemists, physicists, and materials scientists. Especially silver materials with zero-, one-, or two-dimensional nanostructures such as monodisperse nanoparticles [103, 104], nanowires [27], nanodisks [105], nanoprisms [106], nanoplates [107], and nanocubes [108] are believed to have great potential for applications in optics, catalysis, and other fields. Reduction routes involved in these studies fall into three broadly defined categories. The first one involves the use of relatively strong reducing agents, such as sodium borohydride [109], hydrazine [110], and tetrabutylammonium borohydride [110] to prepare silver nanoparticles. The second one is the irradiation of the solution containing silver ions with γ -ray [111], ultraviolet or visible light [112], and microwave [113] and ultrasound irradiation [107, 114]. The third route involves heating the solution of silver salt without commonly used reductants [115] or prolonged reflux silver solution in the presence of a weak reducing agent, such as glucose [116], sodium citrate [117], dimethylformamide (DMF) [118], potassium bitartrate [119], ascorbic acid [120], and alcohols or polyols [121, 122].

A variety of stabilizers or coating agents have been used in the silver particle preparation to achieve the best control of size, size distribution, shape, stability, and solubility of nanoparticles. Thiol derivatives [113] are the most common coating agents employed to stabilize silver colloids, even though aniline [123], long-chain amines [103, 110], surfactants [89], starch [124], and carboxylic compounds [110] have also been used. Polymers such as poly(vinyl pyrrolidone) (PVPo) [36, 121],

fourth-generation poly(amido amine) [125], polyacrylate [126], polyacrylonitrile (PAN) [115], and polyacrylamide (PAM) [111] are also important protective agents, which can effectively control shape, size, and stability of silver nanoparticles. For example, with the refluxing method, PVPo can direct the growth of silver into nanowires [121] and nanocubes [36]. Dickson and coworker have reported that photostable water-soluble silver nanodots created in dendrimers are quite stable and highly fluorescent [127]. Polymer-initiated photogeneration of silver nanoparticles in SPEEK/PVA (SPEEK = sulfonated poly(ether-ether) keton, PVA = poly(vinyl alcohol)) was anticipated to allow direct metal photopatterning [128]. Montmorillonite clay (MMT, as a reducing and stabilizing agent), as lamellar clay, has been used as carriers for silver nanoparticles with good results because of their high ion-exchange capacity, high surface area and sportive capacity, chemical lifelessness, and low or null toxicity [129]. Silver nanoparticles were synthesized onto the surface of MMT by a simple microwave-assisted process from an aqueous solution of silver nitrate; silver nanoparticles with a narrow size distribution on MMT surface were obtained without using any reducing agents [130].

The chitosan-mediated aqueous synthesis method was used for the preparation of high-yield monodisperse multibranched shaped gold-coated iron oxide nanoparticles. The growth of gold coating was achieved in the presence of chitosan and silver ions at room temperature. The plasmon band can be tuned with increasing branch length and gold shell thickness [131]. Further [132] have been synthesized silver nanoparticles protected with bovine serum albumin (BSA) where the BSA itself functions as the reducing agent leading to an undesired protein oxidation. Additional reports have also documented that BSA is able to interact with AgNP electrostatically [133] affecting the binding capacity of the protein with small molecules [133]. Nevertheless, research on the interaction between human serum albumin (HSA), the most abundant protein in the human plasma [134] and AgNP has been scarcely explored [135] though a deep understanding of the phenomenon is relevant for potential biomedical applications. It has also been shown that HSA can effectively interact with quantum dots and gold nanoparticles [136].

Palladium constitutes the most important model system for fundamental studies of metal-hydrogen interaction, which is central in areas such as hydrogen storage [137], heat storage [138], metal hydride batteries [139], hydrogen sensors [140], smart windows [141], and switchable mirrors [142]. Hydrogen forms a stable hydride with Pd, basically without activation barriers. During absorption, H₂ dissociates on the Pd surface and subsequently occupies surface, subsurface, and interstitial lattice sites according to their specific energetics.

The used surfactants find their way to various environmental segments and thus pose serious health hazards. They have the ability to adsorb strongly onto negatively charged suspended particulates and sludge. Intensive investigations have been carried out on their behavior, fate, and biological effects [143]. Long exposure to quaternary ammonium compounds (QACs) can cause sensitization, hemolysis, and toxic effects by all routes of exposure including inhalation, ingestion, dermal application, and irrigation of body cavities.

Polymer-based drug delivery systems emerged from the laboratory bench in the 1990s as a promising therapeutic strategy for the treatment of cancer and other devastating diseases [144]. Polymer–drug conjugates are nanosized hybrid constructs that covalently combine a bioactive agent with a polymer to ensure not only its efficient delivery to the required intracellular compartment but also its availability within a specific period of time. It has already been demonstrated that polymer–drug conjugation promotes tumor targeting by the enhanced permeability and retention effect and its capability of escaping from reticuloendothelial system.

2.2 Precursors and Their Conjugates

Nanoparticles typically grow in nonequilibrium conditions, and their final shapes are influenced by many factors contributing to the kinetics of growth. Factors such as the size, structure, composition of the seed, nature and concentration of metal precursor and reducing agent, molar ratio of precursor to additives, the selective adsorption of additives to different crystal facets, contact with an external support are all clearly capable of influencing the kinetics of particle growth and, hence, the particle morphology. The effects of these factors on the particle morphology are usually quite complex and are not yet completely understood. Therefore, it is a little early to formulate any general mechanism for growth in metallic nanocrystals. However, some preliminary trends have started to evolve. The basic principle of realizing anisometric growth in nanoparticles is that (synthesis) conditions have to be created so that the growth kinetics does not favor equal growth of all facets of the growing nanocrystal. A simple strategy is to use templates (rigid matrices) that will confine particle growth in various directions. When there is no physical template, the nature of the seed and/or the reaction kinetics must ensure dimension-specific growth during the particle formation. In addition to several polyhedral shapes, nanoparticles with highly anisotropic rod-, wire-, plate-, disk-, belt-, ribbon, branched-, or flowerlike morphologies have been prepared. In the related fields, it is essential to gain deeper understanding of the role of nanosizing because nanomaterial engineering provides a powerful means to optimize material performance [145].

The preparation of NMNPs by a chemical reduction approach contains two major parts: (i) reduction using agents such as borohydrides, aminoboranes, hydrazine, formaldehyde, hydroxylamine, saturated and unsaturated alcohols, citric and oxalic acids, polyols, sugars, hydrogen peroxide, sulfites, carbon monoxide, hydrogen, acetylene, and monoelectronic reducing agents including electron-rich transition-metal sandwich complexes; (ii) stabilization by agents such as trisodium citrate dihydrate, sulfur ligands (in particular thiolates), phosphorus ligands, nitrogen-based ligands (including heterocycles), oxygen-based ligands, dendrimers, polymers, copolymers, and surfactants (in particular cetyltrimethylammonium bromide, CTAB). The in situ synthesized gold nanoparticles are also used for the seed-growth or further functionalization. Bolaamphiphiles (also known as bolaform

surfactants, bolaphiles, or alpha-omega-type surfactants) are amphiphilic molecules that have hydrophilic groups at both ends of a sufficiently long hydrophobic hydrocarbon chain. Compared to single-headed amphiphiles, the introduction of a second head- group generally induces a higher solubility in water, an increase in the critical micelle concentration (CMC), and a decrease in aggregation number. The aggregate morphologies of bolaamphiphiles include spheres, cylinders, disks, and vesicles. Bolaamphiphiles are also known to form helical structures that can form microtubular self-assemblies.

The formation and stabilization of silver nanoclusters in solution have been accomplished in various ways (Figs. 2.1, 2.2 and 2.3) [146–149]. The proper choice of parameters for the reaction, including the temperature, the reducing method, the stabilizers, and the initial ratio of metal salt (precursor) : stabilizer (capping agent, poly(methacrylic acid), surfactant, surface-active additive (mercaptosuccinic acid, DNA oligonucleotides, etc.)), reaction medium (water, water/ethanol, and ethanol) plays a crucial role in the successful synthesis of metal nanoclusters. Small variations in the synthetic procedure may change, for example, the collective properties such as fluorescent plasmonic silver nanoparticles to larger nonfluorescent plasmonic silver nanoparticles. Despite the many reports of the last few years about the synthesis of silver nanoclusters, it remains difficult to design general rules for the synthesis of silver nanoclusters, as similar reagents and reaction conditions may lead to silver nanoparticles instead of nanoclusters.

The activation of the reaction to produce silver nanoclusters can be performed following several routes. The silver ions from dissolved silver salts can be reduced, either by a chemical reductant (e.g., sodium borohydride, sodium hypophosphite), by light (photoreduction with visible or ultraviolet light), or by γ -rays (by radiolysis of water). The chemical reduction and the photoreduction are the most commonly used methods. The radiolytic method was also used to produce silver nanoclusters in solution [150]. It is well known that the specific properties of silver nanoclusters, such as the stability and fluorescence quantum yield, depend largely on the scaffold

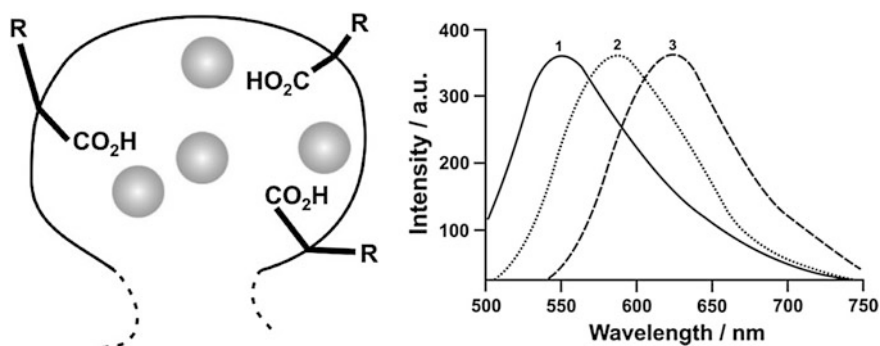


Fig. 2.1 Schematic drawing of silver nanoclusters protected by carboxyl groups of poly (methacrylic acid esters) where R means alkyl ester (*left panel*). Emission spectra of the samples imaged [water (1), water/methanol (2) and methanol (3)] [146]

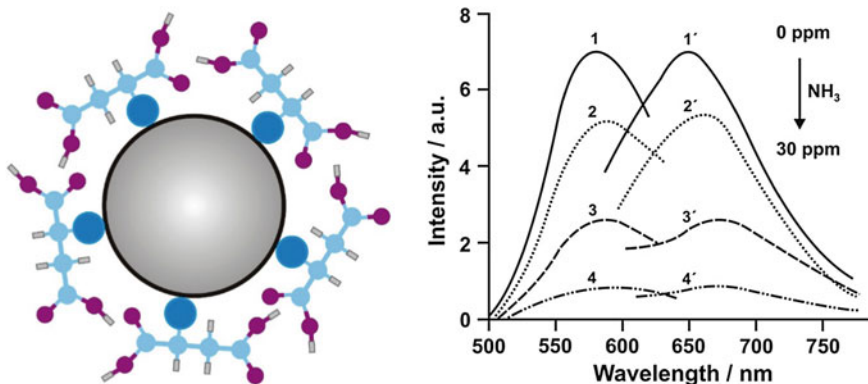


Fig. 2.2 Silver nanoclusters prepared by interfacial etching from silver nanoparticles and stabilized with small molecules (i.e., mercaptosuccinic acid). Fluorescence quenching by addition of quencher (NH₃) [147]

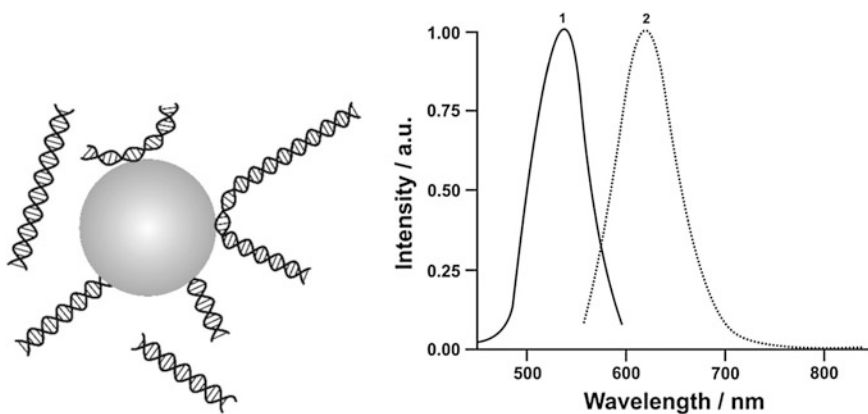


Fig. 2.3 Representation of silver nanoclusters encapsulated in DNA oligonucleotides. Emission spectra of the sample, showing red emitters [148, 149]

used during reduction. The largest fluorescence quantum yield reported for silver nanoclusters prepared in organic scaffolds is achieved using nucleic acid (quantum yield of 64%) [151] while polyacrylates provide stable solutions over years (Figs. 2.1, 2.2 and 2.3) [152]. The sensitivity of silver nanoclusters to the local environment can be exploited for sensing purposes, though it represents a difficulty when designing the synthesis, the proper recipe for the production of silver nanoclusters with a certain scaffold might not be useful when using a different scaffold. Silver nanoparticles larger than 2 nm exhibit plasmon resonance effects and typically do not present fluorescence. However, there are recent reports about luminescent silver nanoparticles. The emission of light from large silver particles is

likely produced from surface-bound nanoclusters or subnanodomains within silver nanoparticles. For gold nanoclusters, the ligands play a major role in enhancing the fluorescence of the nanoclusters in two different ways, by charge transfer from the ligands to the gold core through direct bonding or by direct donation of delocalized electrons of electron-rich atoms or groups of the ligands to the gold core [153]. In the case of silver, the role of ligands or scaffolds on the fluorescence properties is not yet understood.

The nature and concentration of a precursor affect the particle formation in various ways [154–156]. For example, while making platinum nanoparticles through hydrogen reductions of three different platinum precursors ($\text{K}_2[\text{Pt}(\text{C}_2\text{O}_4)_2]$, K_2PtCl_4 , or K_2PtCl_6), Fu et al. [157] have observed that nanoparticles prepared from $\text{K}_2[\text{Pt}(\text{C}_2\text{O}_4)_2]$ exhibit quite narrow size and shape distributions and the selectivity of cubic nanoparticles is greater than 90%. Yu and Xu [156] reported that the use of K_2PtCl_6 and K_2PtCl_4 has a strong influence on the particle-formation reaction and the particle morphology. The result of the synthesis with K_2PtCl_4 was difficult to reproduce due to rapid hydrolysis of the Pt(II)-precursor (K_2PtCl_4) in aqueous solution unlike Pt(IV)-precursor (K_2PtCl_6) [158].

One common method of platinum nanoparticle formation is the in situ reduction of platinum salts by reducing agents to produce a nanoparticulate powder [159], which can then be supported on a low-cost, high-surface-area support. This method has been previously discussed in the literature, and a number of different reducing agents have been employed, for example, formate, formaldehyde, hydrazine, borohydride, formic acid, sodium citrate, and sodium thiosulfate [160]. The alkoxide route allows the properties of the platinum nanoparticles to be easily optimized, by varying the amount of water employed, the ratio of reactants, the synthesis temperature, and the time; the resulting film thickness and porosity can also be modified by varying the substrate withdrawal rate from the sol, the number of coatings, and the film drying temperature and time. The specific synthesis used here for platinum sol formation was shown to produce a precipitate phase and a sol containing suspended metallic PtNPs ca. 1–3 nm in diameter. The purpose is to characterize all of the species formed in the synthesis of several hexachloroplatinic acid (HCPA)/sodium ethoxide (NaOC_2H_5)-formed Pt sols. As well, a mechanism of in situ Pt sol formation via HCPA reduction by NaOC_2H_5 is proposed, with a goal of enhancing the yield of PtNPs for use as an electrocatalyst in fuel cell reactions. Considering the reactants employed in the synthesis, both metallic Pt and NaCl, among other species, can be expected to form (Eq. 2.2). As neither of these is appreciably soluble in ethanol, it was anticipated that both would be found, to varying extents, in the precipitate phase [161].



It was that two phases appear: a precipitate, which ranges from white to black in color, depending on the HCPA to ethoxide ratio, and a yellow- or orange-colored solution phase. From the cyclic voltammetry, X-ray diffraction (XRD), and thermal gravimetric analysis/differential scanning calorimetry (TGA/DSC) results, it has

been shown that the precipitate is composed entirely of small platinum particles (average diameter of 6 nm) and NaCl. The TGA/DSC data showed that the darker precipitates contain a higher percentage of metallic Pt than do the lighter-colored ones. As well, in the optimized sol synthesis (type 1, with a 2:1 sodium ethoxide-to-HCPA ratio), only 1% of the Pt is lost to the precipitate. Electrochemical and inductively coupled plasma spectroscopic results showed that, of the Pt species retained in the sol, 75% was in the form of platinum nanoparticles (1–3 nm diameter) and 25% existed in a Pt(II) form (seen by X-ray photoelectron spectroscopy (XPS) and X-ray absorption near-edge spectroscopy (XANES)). The Pt(II) species was identified, by NMR spectroscopy, as being a Na^+ analogue of Zeise's salt $[\text{KPtCl}_3(\text{C}_2\text{H}_4)]$, which exhibited a greater stability in both ethanol and air than the typical K^+ form of Zeise's salt. The $\text{NaPtCl}_3(\text{C}_2\text{H}_4)$ species, which arises from a side reaction of H_2PtCl_6 and ethanol, rather than as an intermediate formed during the in situ Pt(IV) reduction reaction, may serve as a stabilizer for the PtNPs in the sol phase. The mechanism of PtNP formation from the ethoxide/hexachloroplatinic acid synthesis is proposed to involve a metathesis reaction (a chloride in H_2PtCl_6 is exchanged with an ethoxide group from NaOC_2H_5 , resulting in an unstable $\text{PtCl}_5(\text{OC}_2\text{H}_5)^{2-}$ intermediate and NaCl), followed by a hydride elimination step, producing acetaldehyde and $\text{PtCl}_5\text{H}_2^-$. Finally, a rapid reductive elimination step produces HCl and PtCl_4^{2-} . The process is repeated, reducing the Pt(II) species to Pt(0) nanoparticles.

The typical route for solution-phase synthesis of PtNPs is the simple reduction of metal salts. A wide range of reducing agents have been used in colloid-chemical synthesis of metal nanoparticles of practically all transition metals. For example, H_2 or hydrazine, hydroxyl amine, hydrides (e.g., NaBH_4), ascorbic acid (AA) or ascorbate, citric acid or citrate, oxidizable polymers [e.g., polyvinylalcohol (PVA)], solvents (such as alcohols, aldehydes, and DMF), etc., have been used to prepare various NMNPs [162]. Depending on the reduction potentials of the metal precursor and the reducing-agent systems, reduction can occur at room temperature or at elevated temperatures [163]. Hydrogen is one of the most widely used reducing agents to prepare palladium and platinum nanoparticles. For example, the first shape-controlled colloid-chemical synthesis of platinum nanoparticles used hydrogen reduction of K_2PtCl_4 in the presence of sodium polyacrylate (NaPA: $M_w \sim 2100$) [156, 158]. Similar reduction techniques have been used by several other authors to prepare differently shaped platinum nanocrystals in the presence of a number of other capping polymers [156, 157].

The alcohol-reduction process introduced by Toshima et al. is widely used for the preparation of colloidal noble metals [164]. Alcohols with alpha-hydrogen atoms are oxidized to the corresponding carbonyl compound during the metal-salt reduction. A variation of the alcohol method is found in Figlarz's polyol method, which consists of refluxing a solution of the metal precursor in ethylene glycol or larger polyols [165]. Xia et al. have used this method to synthesize a plethora of anisometric NMNPs [166]. Like alcohols, DMF has been used to reduce Ag^+ ions forming various-shape silver nanoparticles [155]. Reducing agents are not equally effective in generating anisometry in nanoparticles. Often, milder reducing agents

are prescribed for generating anisometric particles [167]. Beyond mere reduction of metal ions, reducing agents affect the nucleation and growth as well as stabilization of nanoparticles [168].

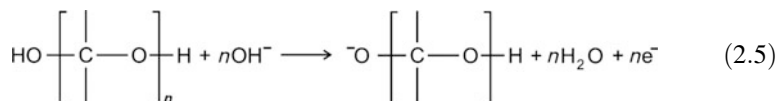
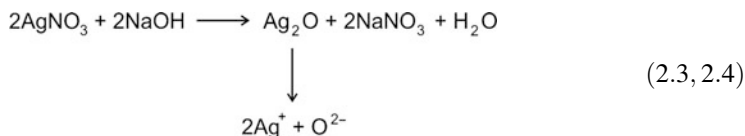
The strength of the reducing agent used in Brust–Schiffrin method is much larger than that of citrate used in the Turkevich method, and according to Marcus theory, the reaction rate in gold nanoparticles synthesis using sodium borohydride (NaBH_4) is much larger than that of the Turkevich gold nanoparticle synthesis using citrate reduction. A direct consequence is that the size of the AuNPs synthesized using the borohydride reductant is much smaller than that of Turkevich method using the citrate reductant. In general, citrate plays a role as a stabilizing agent with preparations of gold nanoparticles requiring relatively high temperatures due to its weak reducing strength. The method pioneered by Turkevich et al. is the simplest one available. In general, it is used to produce modestly monodisperse spherical gold nanoparticles suspended in water of around 10–20 nm in diameter. Larger particles can be produced, but this comes at the cost of monodispersity and shape. It involves the reaction of small amounts of hot chloroauric acid with small amounts of sodium citrate solution. The colloidal gold will form because the citrate ions act as both a reducing agent and a capping agent. To produce larger particles, less sodium citrate should be added. The reduction in the amount of sodium citrate will reduce the amount of the citrate ions available for stabilizing the particles, and this will cause the small particles to aggregate into bigger ones (until the total surface area of all particles becomes small enough to be covered by the existing citrate ions). Slot discovered a new way to prepare gold nanoparticles using a mixture of tannic acid/citrate solution whereby tannic acid plays the role of a reducing agent instead of citrate, and the AuNPs are obtained at 60 °C [169]. Then, Natan's group introduced a method using citrate as a stabilized agent only and borohydride as a reducing agent [170]. The AuNPs were obtained upon adding the NaBH_4 /citrate mixture into the HAuCl_4 solution at room temperature. With this method, the size of AuNPs is tailored to 6 nm, which compares with sizes beyond 20 nm using the traditional Turkevich method. Remarkable modification of the Turkevich method involved the reversed order of addition that was conducted by adding HAuCl_4 to the citrate solution, producing monodispersed AuNPs with relatively small size (less than 10 nm) [171]. The further simple method generates nearly monodisperse “naked” gold nanoparticles in water. Precisely controlling the reduction stoichiometry by simply adjusting the ratio of NaBH_4 – NaOH ions to HAuCl_4 – HCl ions within the “sweet zone,” along with heating, enables reproducible diameter tuning between 3 and 6 nm. The aqueous particles are colloiddally stable due to their high charge from the excess ions in solution. These particles can be coated with various hydrophilic functionalities, or mixed with hydrophobic molecules for applications in nonpolar solvents. Interestingly, in nonpolar solvents the nanoparticles curiously remain highly charged and self-assemble on liquid droplets to form 2D monolayer films of monodisperse nanoparticles.

There are several methods for the preparation of silver nanoparticles such as citric acid reduction, electrochemical synthesis, photoreduction, and radiation (see also above). However, silver nanoparticles prepared from these methods can only

be kept for a maximum of 2–3 months [172]. Many experiments have shown that the growth of silver nanoparticles in solution is sensitive to the presence of citric acid or sodium citrate but the exact role of citric acid is still unidentified. Later, [173] reported that using citric acid as a reducing agent made the reduction reaction take one week longer and led to a wide size distribution. They also reported that the use of sodium citrate did not result in the formation of silver nanoparticles. As far as stabilizers are concerned, citrate ions can bind on silver surfaces for shape control, but their ability to stabilize silver particles is weaker than thiols [174]. Nowadays, a molecule which can act both as a reducing and capping agent is preferred so that the reaction takes place in one step and there is no need for an external reducing agent. This will reduce the number of steps involved in metal nanoparticle synthesis. The physical method involves radiation reduction of silver ions by γ -ray, microwave, ultraviolet, or visible light [175]. Chemical reduction in solution is advantageous over other processes, because of its simplicity, low reaction temperature, and solubility of metal salts in water. The most used reducing agents are NaBH_4 , ethylene glycol, DMF, dimethylacetamide, and formamide [176].

Several methods have been used to synthesize silver nanoparticles such as chemical reduction; Tollen's reagent; photoreduction; and biochemical, sol-gel and polyol approaches [177]. Paraformaldehyde and citric acid are used as stabilizing and reducing agents for synthesizing silver nanoparticles through the reduction in silver ions by the oxidation of hydroxyl groups of paraformaldehyde to aldehyde groups using strong base, NaOH . The addition of silver nitrate to the NaOH solution leads to the formation of Ag^+ as $[\text{Ag}(\text{H}_2\text{O})_4]^+$, which then change to silver oxide (Ag_2O) through the reaction of OH^- ions with Ag^+ ions. A dark cream solution is produced because of the formation of a large amount of silver oxide (Ag_2O) sediment (Eq. 2.3) [178].

Paraformaldehyde is deprotonated $[-\text{O}(\text{CH}_2\text{O})_n\text{H}]$, and electrostatic interaction between silver ions and free deprotonated paraformaldehyde shielded the formed nanoparticles and grabbed silver clusters to the nanoparticles (Eq. 2.3). Increasing temperature-using microwave in the presence of NaOH solution (pH 12) leads to fast hydrolysis paraformaldehyde to oligomers that capped more Ag^+ ions and cause high dispersion on template surface (Eq. 2.4). The addition of citric is obligatory because of the removal silver ions by NaOH (redox reaction), which inhibits further reduction reaction of the silver particle surface (Eqs. 2.5 and 2.6) [179].





Liz-Marzan et al. [155] have shown that silver nanoparticles can be prepared in DMF without adding any reductant. It has been suggested that the reduction rate can be enhanced at high temperatures. Because most of the organic reactions take place in organic solvents, it is desirable to develop synthetic methods that lead to the formation of particles having different morphology in addition to the stabilization of metal nanoparticles in such solvents. In addition, if one can design a synthetic method to prepare different morphological particles in the same medium without adding reductants from outside, this may have its own important implications. Formamide is one of the most common solvents used to study various processes such as formation of metal nanoparticles, interaction with alcohols. [180]. It is known that formamide–water and formamide–methanol complexes can serve as model systems for protein–water and protein–solvent interactions. Photocatalytic oxidation of volatile organic chemicals (VOCs) constitutes one of the most promising methods for the removal of these pollutants in an enclosed atmosphere. Generally, metal oxides are being explored for such purposes. As silver is known to have bactericidal properties, it is important to assess its effect on VOCs. We have described the preparation of silver nanoparticles by reduction of silver ions with formamide in the absence and presence of stabilizers such as PVPO and SiO₂ nanoparticles. In addition, attempts have been made to see the effect of addition of methanol, VOCs, and a complexing agent on the stability of silver nanoparticles. The reaction of silver nanoparticles with CHCl₃ is indicative of the strong reducing power of the particles. As the nanoparticles have more surface atoms, the unsaturation at the surface is very high. In the presence of an organic molecule, which is an electrophile, the surface atom acquires an excess positive charge and the rest of the nanoparticles a corresponding negative charge. In the presence of oxygen, this excess negative charge is removed and the oxidation of the silver particles can proceed. This could be the reason for observing fast oxidation of silver particles in an aerated solution as compared to that in a N₂-bubbled solution. Similarly, the reactivity of silver nanoparticles with toluene was investigated. After addition of toluene to a silver dispersion in formamide, the color of the silver sol gradually faded due to oxidation in the formamide layer. However, in a N₂-bubbled solution, the oxidation of particles was very slow. It is known that oxidation of toluene leads to the formation of benzaldehyde. As metal particles can act as a sink for electrons, it appears that in the presence of silver particles, there is a possibility of oxidation of toluene, which is facilitated by the presence of oxygen [181].

The use of amine–borane complexes is essential for the syntheses of monodisperse metallic nanoparticles. Compared to commonly used reducing agents (e.g., NaBH₄, LiBH₄), amine–borane complexes have a weaker reducing ability, which can slow the reducing rate of gold cations and allow control over the growth of nanoparticles [182]. Upon the addition of strong reductants, such as NaBH₄, gold cations are reduced rapidly, resulting in an immediate color change of the reaction mixture from colorless or yellow to dark red. With the use of weaker reductants

applied in these syntheses, a much slower but continuous color change from colorless to yellow, pink, brown, and finally to purple–red is observed, which indicates a relatively slow reducing rate of Au(I). In addition to tert-butylamine–borane, other amine (i.e., triethylamine, morpholine, and ammonia)–borane complexes can be used. While the triethylamine complex is a reducing agent comparable to the tertbutylamine complex, the morpholine complex exhibits much weaker reducing ability and requires longer reaction time to complete the reaction. In comparison, the reducing ability of ammonia–borane is much stronger, so that it is difficult to obtain nanoparticles with a narrow size distribution.

The reducing power of the amines of several different structures was studied by Newman and Blanchard [183], who showed, very clearly, that the oxidation potential of the reducing agent should lie between the oxidation of Au(0)–Au(I) and the reduction of Au(III)–Au(0) for the reaction to proceed. Outside this range, the reaction is not spontaneous. Multifunctional amines and nitrogen-containing polymers have also been tested for the synthesis of gold nanoparticles [184, 185]. Indeed, the potential scan started immediately above the point at which the reduction of Au(III) occurs and firstly toward the cathodic direction. At pH 4.0 (Fig. 2.4, left panel), the reduction of Au(III)–Au(0) occurs at 0.72 V (peak I), and the oxidation of the main product Au(0) generated in this process appears in the opposite scan at 1.14 V (peak III).

Under the same experimental conditions, the cationic polyelectrolyte form of the block copolymer does not exhibit prominent electrochemical activity, and no more than a weak oxidation signal appears at 1.00 V (shoulder I*). In principle, the polymer oxidation potential is located within the range required for a spontaneous redox reaction with Au(III) to occur, but still no AuNPs are formed. One can attribute this finding to the onset oxidation potential of Au(0) of 0.92 V (arrow

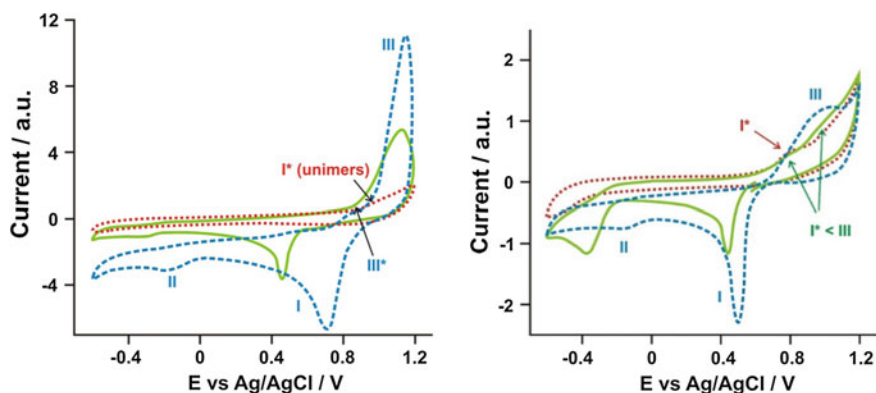


Fig. 2.4 Cyclic voltammograms recorded at 50 mV/s in aqueous media during selected experimental steps that ultimately lead to the spontaneous AuNP nucleation and growth mediated by pH-responsive triblock 1 copolymer, as indicated. [Au(III)] = 0.275 mM; [NR₃ groups] = 0.275 mM; $C_{\text{triblock1}} = 1.0 \text{ mg.mL}^{-1}$; *Left* pH 4.0 with 0.1 M KCl as electrolyte, *Right* pH 6.8 with 0.1 M KH₂PO₄/K₂HPO₄ as electrolyte [186]

labeled III*), which is lower than that of the polymer, implying that Au(0) would be oxidized before the polymer. The latter, however, strongly influences the reduction of Au(III), the potential of which shifts toward cathodic values from 0.72 V down to 0.45 V in the presence of the electrochemically inert cationic polyelectrolyte.

When the pH is controlled by using phosphate buffer solutions at pH 6.8, the electrochemical potentials of reactions involving the reactants Au(III), Au(0), and polymer micelles shift to lower values (Fig. 2.4, right panel). Au(III) is reduced to Au(0) at 0.50 V, which, in the absence of polymer, is oxidized at 1.00 V. Polymeric micelles undergo an oxidation reaction that gives a current density increase with a peak at 0.81 V. The oxidation potential of the polymer also lies within the range necessary for a spontaneous redox reaction with Au(III) to occur. When the individual cyclic voltammograms of Au(III) and polymer micelles are compared, one would expect the reaction not to take place because the onset of the polymer and Au(0) oxidation processes superimpose at 0.66 V.

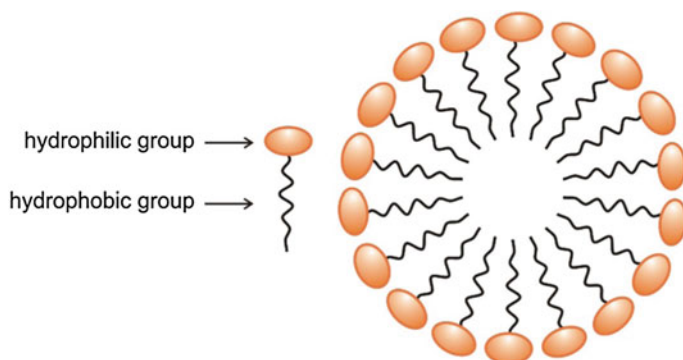
The voltammogram recorded for a mixture of Au(III) and polymer reveals interesting new features. On addition of this buffer solution, the amino groups of the PDPAEMA (poly2-(diisopropylamino) ethyl methacrylate) segment are neutralized, and the polymer is rendered amphiphilic. Furthermore, the polymer chains become better electron donors through the presence of a lone pair of electrons on the nitrogen atoms of the amino groups after deprotonation. The self-assembled micelles feature a hydrophobic core with nitrogen atoms coordinated to Au(III); the affinity of gold for nitrogen is higher than that for the other possible atom-donor species in solution. These core@shell-type nanostructures can interact with the electrode surface and exhibit electrochemical activity in spite of having a stabilizing interface (shell) that is electrochemically inactive. The coil-like chains forming the hydrated shell can deform or rearrange to facilitate contact with the electrode surface. In fact, a few studies have been carried out on redox-active block copolymer micelles in which electrochemical reactions involved centers of an organic or organometallic nature, located in the hydrophobic core [187]. Depending on the reaction pathway and products, spherical micelles can be either disrupted or transformed into other morphologies [188].

The most important information obtained from the voltammogram recorded for the mixture is that the oxidation potential for the polymer in the form of micelles (peak I* micelles) is lower than the oxidation of Au(0) (peak III). As a result, gold nanoparticle synthesis is mediated solely by polymers with tertiary amino groups situated in the micelle core (the reaction microenvironment), without the need for any other reactant. Cyclic voltammograms recorded for AuNP@triblock 1 (poly(ethylene oxide)-*b*-poly(2,3-dihydroxypropyl methacrylate)-*b*-poly[2-(diisopropylamino) ethyl methacrylate] (PEO-*b*-PDHPMA-*b*-PDPAEMA) [186] after reaching a stable plateau in the characteristic absorption wavelength demonstrated that the Au(III) species were almost quantitatively converted into nanoparticles, since no reduction peak typical of their reduction was observed. Essentially, the same behavior was also observed using sodium tetraborate buffer solutions at pH 9.1.

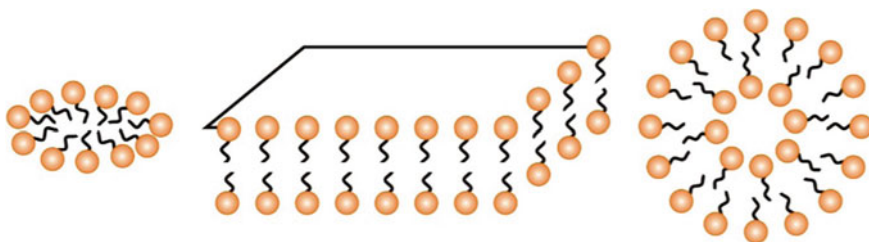
The controlled self-assembling of amphiphilic block copolymers into micellar structures (Schemes 2.2, 2.3, 2.4, 2.5 and 2.6) has attracted substantial interest for

various potential applications, including particle syntheses, drug and gene delivery, catalysis, templates, metal particle synthesis, and biosensors [189–192]. Rationally designed molecular building blocks allow for the precise control of particle size and morphology of the supramolecular aggregate, and various defined structures, including spherical micelles, rodlike micelles, or vesicles [193, 194].

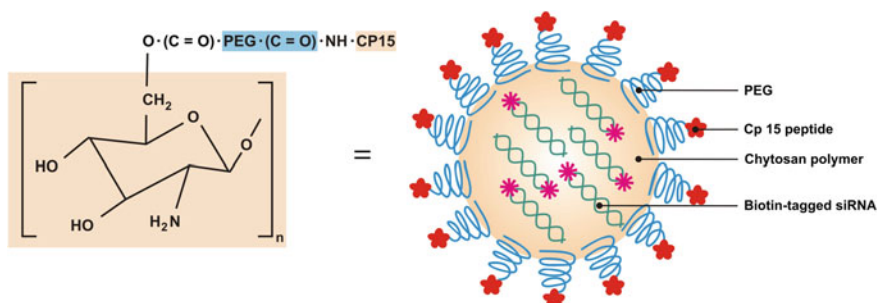
Vast studies have concerned aqueous solutions of the amphiphilic “pluronics” type of triblock copolymers, PEO-PPO-PEO, for pharmaceutical use and drug delivery systems [195]. It is well established that the pluronic copolymers with higher PEO/PPO [(poly(ethylene oxide)/poly(propylene oxide))] ratio self-assemble into micelles composed of a PPO-rich core and a PEO-rich corona above the critical micellar concentration and a critical micellar temperature (CMT) [196]. Amphiphilic block copolymers (AB or ABA-type) with large solubility differences between hydrophilic and hydrophobic moieties, in aqueous medium are able to self-assemble into polymeric micelles characterized by mesoscopic size range. These structures consist of water-insoluble cores and water-soluble shells. Depending on blocks’ length, the core can assemble into various supramolecular structures characterized by different morphologies (Scheme 2.7). Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymers are well known as dispersion stabilizers and templates for the synthesis of mesoporous materials and nanoparticles [197]. Variation of the PEO-PPO-PEO block copolymer molecular characteristics, concentration, and temperature allows for unique tunability of block copolymer self-assembly in the presence of selective solvents such as water. It was found that PEO-PPO-PEO block copolymers can act as very efficient reductants/stabilizers in the single-step synthesis and stabilization of gold nanoparticles from hydrogen tetrachloroaurate(III) hydrate (in air-saturated aqueous solutions) at ambient temperature in the absence of additional reductant or energy input [198]. This synthesis proceeds fast to completion and is environmentally benign and economical since it involves only water and nontoxic commercially available polymers (poloxamers or pluronics). The gold nanoparticle dispersions remain highly stable for several months. On the contrary, PEO



Scheme 2.2 Schematic of self-assembly of copolymer blocks into micelles



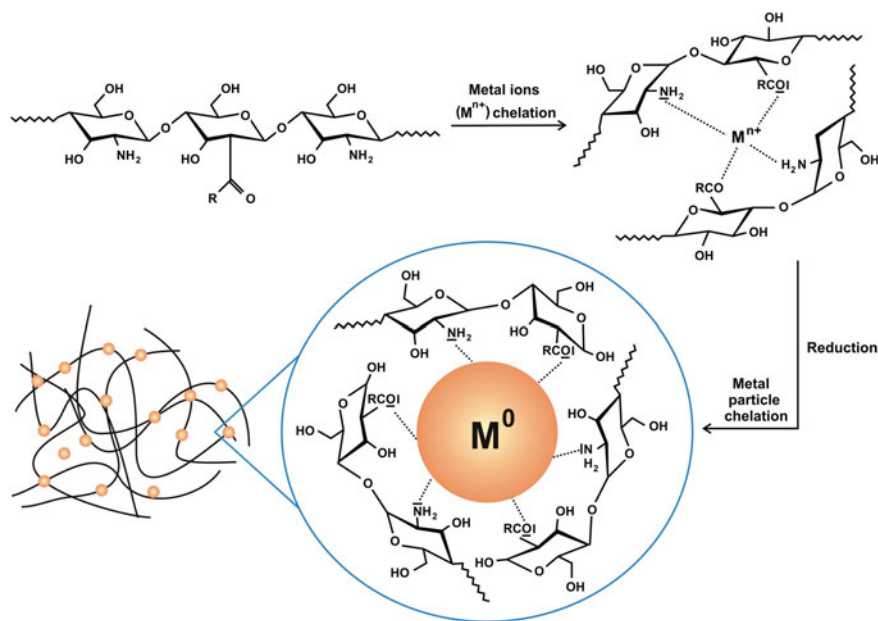
Scheme 2.3 Various defined structures, including disk-like, lamellar, and spherical vesicles



Scheme 2.4 Mechanistic view of drug delivery systems

homopolymer, of molecular weight comparable to that of the PEO-PPO-PEO block copolymers, was very slow in producing particles (more than 2 days were needed) and inadequate for their colloidal stabilization. Compared to recently reported single-step methods for gold nanoparticle synthesis, this method offers the advantages of ambient conditions, fast completion, being economical, and resulting in a “ready-to-use” product. The contributions of block copolymer molar concentration, PEO concentration, PPO concentration, and CMC are addressed by examining a range of PEO-PPO-PEO block copolymers. These polymers have the ability to form temperature-dependent micellar aggregates and, after a further temperature increase, gels due to micelles aggregation or packing. Therefore, with these polymers it is possible to mix drugs in the sol state and at room temperature and the solution can be injected into a target tissue. It forms an in situ gel depot at body temperature and provides controlled drug release. A formulation which is in the form of injectable liquid at room temperature, but changes into gel at body temperature, with a pH close to neutrality and having a certain biocompatibility and biodegradability surely represents an ideal system.

In general, different kinds of synthetic copolymers are made of poly(ethylene oxide) as hydrophilic block, and of a wider range of hydrophobic blocks. The combination of different PEO-hydrophobic blocks has given rise to several micelle systems with differing physicochemical properties, such as loading capacity,



Scheme 2.5 Nucleation of metal nanoparticles via complexation of precursors followed by reduction of metal salts by functional polymer [189–192]

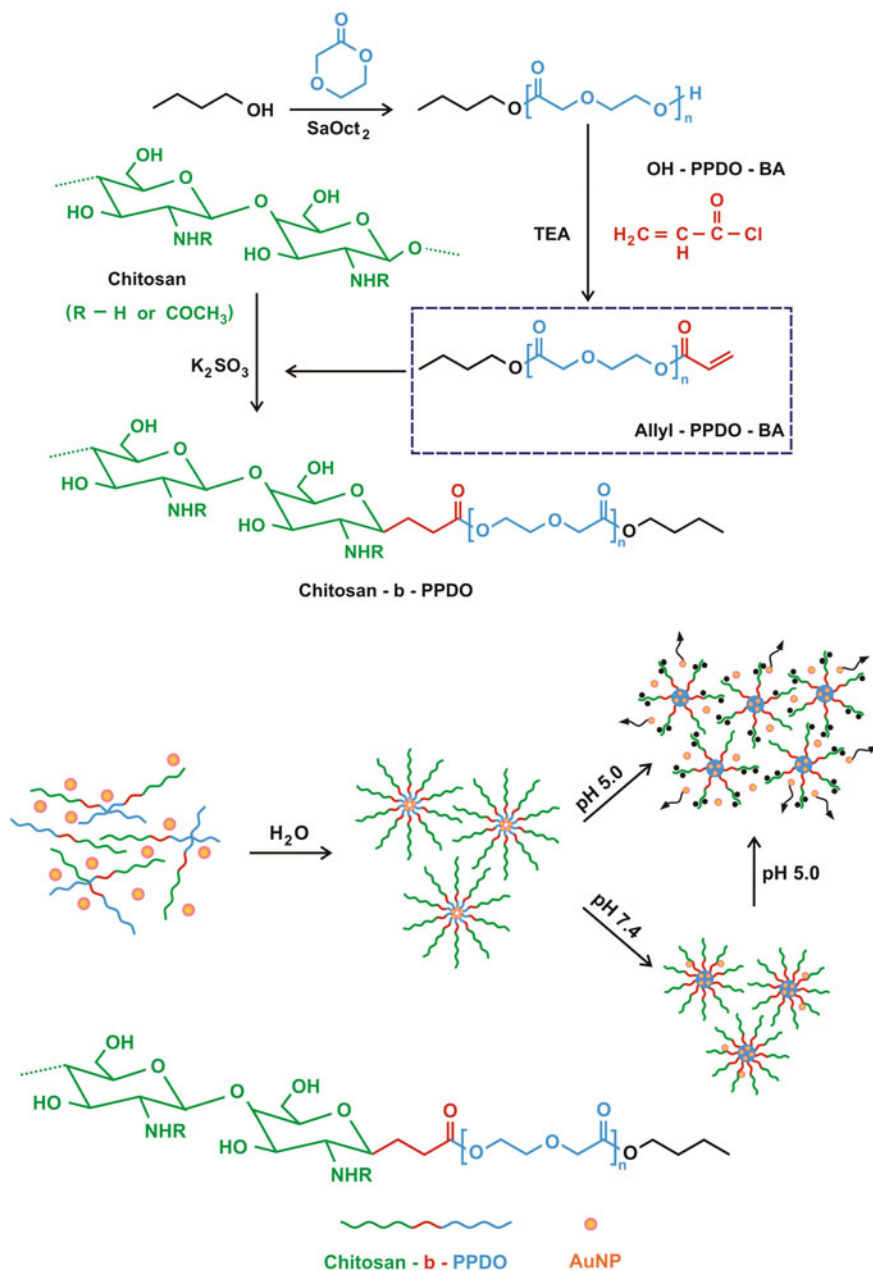
morphology, gel, biodistribution, size, release kinetics, and specificity against different kinds of drugs (Scheme 2.7).

In aqueous systems, the effects of metal ion/stabilizer mixing ratio, reaction temperature, reaction time, and energy input on the formation of colloidal particles typically have been considered. Formation of gold nanoparticles from AuCl_4^- in aqueous PEO-PPO-PEO block copolymer solutions includes three main steps: (1) reduction of metal ions in aqueous block copolymer solution, (2) absorption of block copolymer on gold clusters because of amphiphilic character (hydrophobicity of PPO) and reduction of further metal ions on the surface of gold clusters, and (3) growth of gold particles and stabilization by block copolymers (refer to Scheme 2.8):

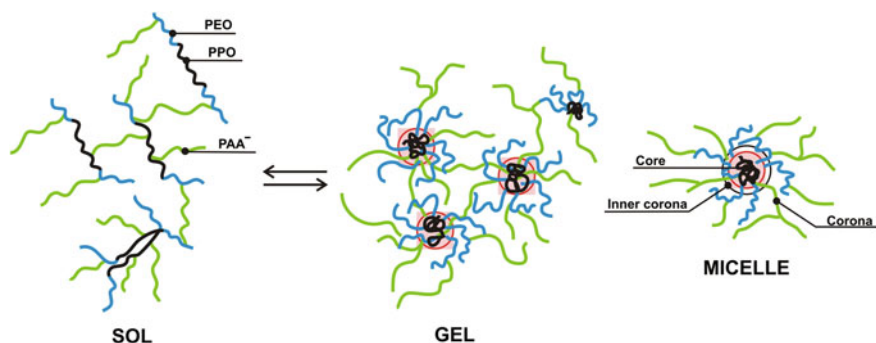
(1) reduction of metal ions facilitated by block copolymers in solution,



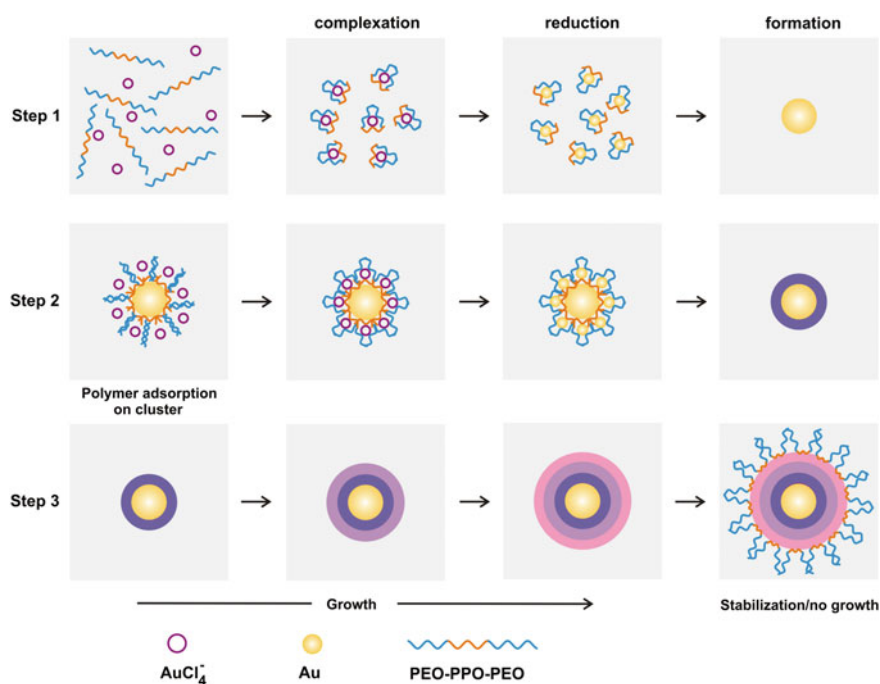
where $(\text{AuCl}_4^-) \cdot (\text{PEO-PPO-PEO})_n$ represents AuCl_4^- ions bound to cavities that are formed from hydrated PEO and PPO coils. Reduction of bound AuCl_4^- ions



Scheme 2.6 Encapsulation of nanoparticles by the micellar aggregation via varied solubility and pH [poly(*p*-dioxanone) (PPDO)] [189–192]

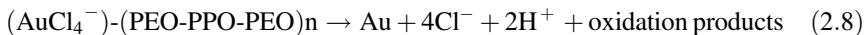


Scheme 2.7 Amphiphilic “pluronics” nanostructures based on $\text{PAA}^- \text{Na}^+$ [197]

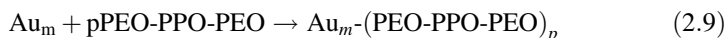


Scheme 2.8 Schematic of proposed mechanism of AuCl_4^- reduction and particle formation [200, 203]

proceeds via oxidation of the polymer by the metal center. Oxidation products (carboxylate groups) have been identified by Fourier transform infrared spectroscopy (FTIR) in PEO homopolymer systems¹ [199] after AuCl_4^- reduction:



Following the formation of gold clusters through reduction of AuCl_4^- ions in solution, block copolymers adsorb on the surface of gold clusters, Au_m , due to the amphiphilic character of the PEO-PPO-PEO block copolymers:



where $\text{Au}_m \cdot (\text{PEO-PPO-PEO})_p$ represents a gold cluster with adsorbed block copolymers. The adsorbed block copolymers can form pseudo-crown ether structures that bind with AuCl_4^- ions, $\text{Au}_m \cdot (\text{PEO-PPO-PEO})_p \cdot \text{AuCl}_4^-$, and facilitate their reduction.

- (2) absorption of block copolymers on gold clusters and reduction of metal ions
comparison of various PEO-PPO-PEO block copolymers reveal that the overall block copolymer (i.e., both PEO and PPO blocks) contributes to AuCl_4^- reduction and particle formation. The third step is the growth of gold particles and stabilization by block copolymers (refer to Scheme 2.8).

PEO is more dominant than PPO in the initial stages of reduction. PPO facilitates block copolymer adsorption on gold clusters and reduction of AuCl_4^- ions on the surface of these gold clusters and/or particles. The difference in particle formation observed between PEO-PPO-PEO block copolymer systems and PEO homopolymer systems is attributed to the block copolymer adsorption and AuCl_4^- reduction processes on the surface of gold clusters and/or particles (steps 2 and 3) [200].

To improve the stability of polymeric micelles against dilution in the stream, various methods, by chemically cross-linking either in the inner core domain or within the outer shell layer, have been developed [201]. For example, Park et al. have reported on the shell cross-linked pluronic micelles using gold nanoparticles that exhibit a reversibly thermosensitive swelling/shrinking behavior [196]. The study on the evolution and morphology transition of the shell cross-linked micelles is, however, scarce. Xu et al. [202] have demonstrated that the gold nanoparticle-stabilized pluronic micelles spontaneously evolve and reassemble into large “vesicular”-like nanocapsules using glutathione as an effective trigger. It was also demonstrated that the evolved nanocapsules showed obvious temperature responsibility.

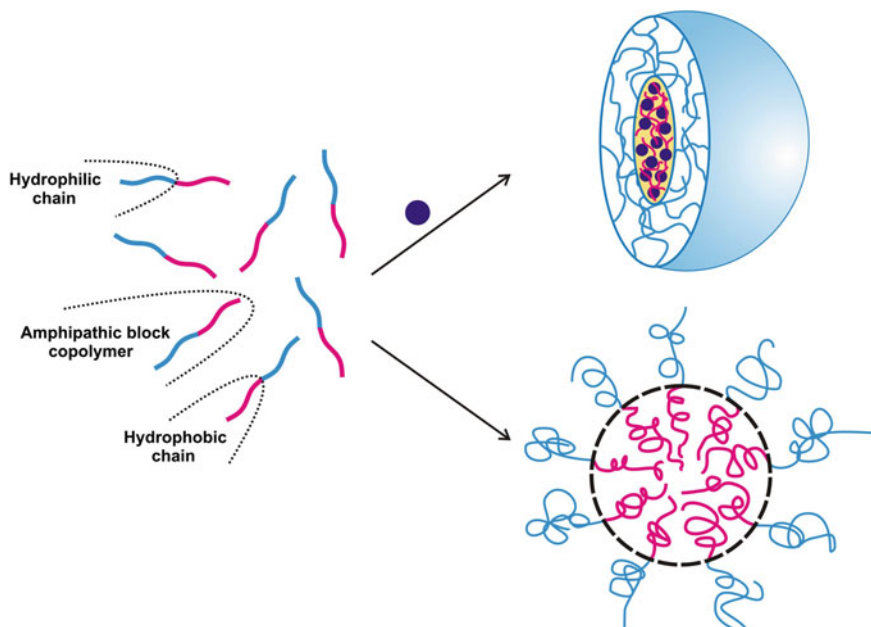
The incorporation of copolymers into the gold nanoparticles fabrication process has led to the interesting discovery that both the formation and the stability of colloids are dictated by the chemical structure of macromolecular chains. Environmentally friendly, single-step/single-phase synthesis of core@shell NMNPs can be mediated by polymers that simultaneously play the roles of reductant and stabilizer while imparting unique properties to the resulting hybrid material (Scheme 2.8). To date, the above strategy has been applied successfully mainly to pluronics and polyacrylates with amino groups, which have a strong ability to coordinate on metal surfaces [203]. The reduction of Au(III) species is induced by

the poly(propylene oxide) (PPO) segment and nitrogen atoms, respectively. Polymer chains chemisorb onto the newly generated particle, being consequently tethered from the surface into the solvent phase. Despite their simplicity (one-pot, two-reactants, and no workup), this class of reactions still offers a number of possibilities in relation to tweaking the experimental conditions (concentration of reactants, polymer composition and architecture, temperature, and additives) to generate particles with controlled dimensions and properties. A comprehensive understanding of the kinetics and chemical environment around the gold cores is obviously relevant in such an endeavor, and more data in this respect are required to provide a clearer picture of these systems.

Furthermore, copolymers (as capping agents) with stimulus responsibility have attracted growing attention due to their diverse self-assembly behavior in response to stimuli, such as pH, temperature, salt [204]. The stimulus responsibility allows for tailoring the supramolecular aggregates with desirable morphologies and properties from the same precursory copolymers (Scheme 2.9). Poly(*N*-isopropylacrylamide) (pNIPAM) is a stimulus responsive polymer that undergoes a reversible, inverse phase transition at a lower critical solution temperature (LCST) of about 32 °C in pure water. In addition to temperature, cosolvents can also cause an inverse phase transition in pNIPAM. For example, the addition of 50% methanol by volume to aqueous pNIPAM solutions leads to cononsolvency, effectively lowering the LCST of pNIPAM to below 0 °C. The functionality of pNIPAM on surfaces can be separated into two categories: (1) triggered changes in polymer conformation and (2) triggered changes in polymer surface energetics. Below the LCST, pNIPAM is hydrated and the chains are in an extended conformational state. Above the LCST, pNIPAM is in a hydrophobically collapsed conformational state. Polymer brushes with triggerable phase-transition behavior, such as pNIPAM, can be exploited in devices on the nano- and microscales, with potential applications for protein affinity separations and in micro- and nanofluidics [205].

It was demonstrated the surface-initiated polymerization of stimulus-responsive pNIPAM brushes from monolayers on gold-coated surfaces. By adopting low methanol concentrations during polymerization, the growing pNIPAM chains were maintained in a hydrophilic and an extended conformational state, yielding thick polymer brush layers. In addition, the prototypical fabrication of nanopatterned, surface-confined, stimulus-responsive pNIPAM brushes in a grafting-from approach using a simple strategy that combines nanoshaving, an SPL (scanning probe lithography) method, with surface-initiated polymerization were presented. The reversible, stimulus-responsive conformational height change of these bulk and nanopatterned polymer brushes is consistent with the behavior of surface-confined polymer chains, where chain mobility is restricted largely to one dimension perpendicular to the substrate. The polymerization and patterning approach is generic and can likely be extended to a wide variety of monomers [206].

The nature of precursor species in actual reaction mixture may not be as simple as it appears from molecular formula. For example, Xia and coworkers reported that



Scheme 2.9 Self-assembly behavior in response to stimuli effect. Via the formation of a nanoparticle proceeds the drug encapsulation [204]

a freshly prepared aqueous solution of AgNO_3 contains trimeric Ag_3^+ or Ag_3 species that acted as nuclei and led to the development of a triangular morphology [207]. The concentration of trimeric clusters of silver decreased as the AgNO_3 solution was aged in air under ambient conditions. Icosahedrons and cuboctahedrons were formed by reducing either Ag^+ ions or complexes such as $[\text{Ag}_2(\text{NO}_3)]^+$ and $[\text{Ag}_3(\text{NO}_3)_2]^+$ with polyvinylpyrrolidone. Further, the by-product ions, molecules, etc., formed from the precursor during particle-formation reaction can, for example, change the pH, the ionic strength, or can influence the activities of tailor-made additives. The seed-nuclei size can be determined by the strength of the metal-metal bonds and the difference between the redox potentials of the metal precursor and the reducing agent used [208]. Specific chemical reactions, such as the disulfide reduction, have emerged as an alternative stimulus for tuning the self-assembling of copolymers. For example, monodispersed polymeric nanocapsules have spontaneously evolved from reducible hetero-PEG PIC (polyion complex) micelle disulfide bond reduction [209].

In a next report, a simple solid-phase asymmetrical functionalization technique was introduced to construct gold nanoparticles with reactive ligands localized on a small confined surface [210]. This approach highlights that (i) the ligands decorated on a spatially limited surface can be used for further chemistry, and the rest of the ligands can be selected to remain unreactive during the coupling process. (ii) It was applicable to a wide size range of nanoparticles, e.g., the functionalization of gold

nanoparticles with the diameter of 16–41 nm was demonstrated. They used 3-aminopropyltriethoxysilane as the bifunctional ligand to “catch” the gold nanoparticles onto the glass substrate. Owing to the strong interaction between the AuNPs and the amino-silanized glass surface, a second ligand with a thiol functional group was required to replace the amino-binding sites under severe sonication so as to “release” the AuNPs from the substrate. However, the introduction of a second ligand to the AuNPs confines further chemistry to some extent. Additionally, biomolecules, such as DNAs and proteins, may be damaged during the sonication process. Therefore, asymmetric AuNPs decorated with biomolecules was almost impossible to be obtained [211].

Coordination chemistry offers simplicity, stable bonding, and ligand-metal specificity, enabling ligand-bearing components to be assembled into supramolecular structures using appropriate metal ions. This approach is particularly compatible with surface chemistry, as binding of metal ions activates the surface toward ligand binding, and vice versa. The use of different building blocks containing similar ligand functionalities provides a universal, LEGO-type binding scheme, where the same chemistry is used for binding different components into a composite nanostructure. This strategy is attractive for LbL schemes, adding one coordinated layer in each step. Murray and coworkers investigated coordinated nanoparticle films prepared by repetitive adsorption of carboxylate-modified AuNPs and divalent metal ions (Cu^{2+} , Zn^{2+} , Pb^{2+}) [212, 213]. In these systems, several nanoparticle monolayers are deposited in each dip cycle, while the interparticle spacing was shown to be lower than expected for coordinative carboxylate-metal ion binding. Chen and coworkers obtained similar results with pyridine-functionalized AuNPs and Cu^{2+} ions, studied by quartz crystal microbalance measurements [214]. These observations suggest that Cu^{2+} -based coordination systems induce insertion of excess ions to the periphery of the nanoparticles, resulting in poorly controlled growth (Scheme 2.5).

As a promising nanobiomaterial, gold nanoparticles have found a burst of research interest in biological applications, for example, transfection vectors, DNA-binding agents, protein inhibitors, and spectroscopic markers [215, 216]. Among the unique features of gold particles, facile place-exchanging reaction makes them well suited for biomedical applications [30]. As the most abundant thiol species in the cytoplasm and the major reducing agent in biochemical processes, glutathione (GSH, a tripeptide is a peptide consisting of three amino acids joined by peptide bonds, L-glutamine, L-cysteine, and glycine) showed special interest for the manipulation of place-exchanging reaction [217]. The glutathione-mediated selective intracellular release system has been developed on the basis of the fact that the intracellular GSH concentration is substantially higher than extracellular levels [217]. GSH is the most abundant low molecular weight thiol (LMWT) and is widely accepted to be the main cellular redox buffer.

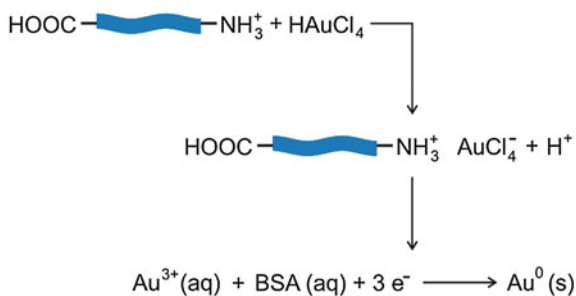
For an effective shape-controlled synthesis, the surface activity of biomolecules at the liquid–solid interface plays a significant role. Molecules which control the overall crystal growth are known as “capping agents,” the term frequently used for specific adsorption of surface-active molecules on selective crystal planes of a

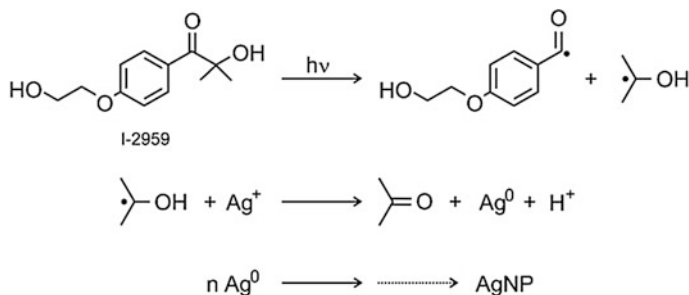
particular geometry [218]. In addition to the stabilizing ability of some stabilizing agents, these additives can also be used as a reducing agent. This is case of bovin serum albumin (BSA) [219] for synthesizing NMNPs. Several other proteins and enzymes have shown the reducing ability of gold and silver ions into their respective nanoparticles [220]. If a stabilizing agent also provides reducing ability, then it becomes quite easy to understand the nucleation process and subsequently shape-directing effects as well. A protein macromolecule contains several amino acids such as cysteine, tryptophan, lysine which can act as weak reducing agents. All these amino acids can reduce gold or silver ions independently even at room temperature (Scheme 2.10).

However, when amino acid is present in a macromolecule, the reducing ability is significantly compromised by the steric screening of other nonreducing amino acids in the vicinity. Then, the reducing ability of a particular amino acid is purely related to its location in the native state of protein. As the globular form unfolds, more and more hidden cysteine amino acids come into contact with the aqueous phase whereby they provide a stronger reducing potential to BSA. Hence, unfolding not only facilitates the reduction but also provides required amphiphilic character necessary for the surface activity to produce desired shape-directing effects and is true for almost all globular proteins. Like PbSNPs and SeNPs, the unfolded BSA is also responsible for the synthesis of gold nanoplates with preserved {100} crystal planes of fcc geometry [219]. High temperature (around 70–80 °C) and sufficient acidic environment provide BSA with enhanced reducing as well as shape-directing abilities which are not observed close to the isoelectric point or room temperature.

HSA instead of BSA can be employed as model for exploring how proteins interact with silver nanoparticle since it has been reported before the different binding capabilities of HSA and BSA in spite of their structural similarities [221] by manipulating the biomacromolecule conformation, and/or selectively blocking NH_2 groups the authors have shown that there is a combination of several non-covalent electrostatic interactions involved in such phenomenon, where NH_2 residues play a key role in the observed poststabilization and synthesis of AgNPs. Alarcon et al. [222] have also explored to what extent surface plasmon band (SPB) excitation with 405-nm light-emitting diode (LED) can affect the protein conformation in the AgNP@HSA hybrid. Ketyl radicals formed by the photolysis of photoinitiator (I-2959) acted as reductants of silver salt leading to the formation of

Scheme 2.10 Schematic of the reducing and stabilizing ability of amino acids [220]





Scheme 2.11 Overall reaction for the formation of silver nanoparticles. Sodium citrate as a stabilizer has been employed [222]

AgNPs. This approach is based on the Norrish Type I photocleavage of carbonyl-type initiator leading to ketyl radicals [223]. Silver cations, Ag^+ , scavenge the $(\text{CH}_3)_2\text{C}^\bullet\text{OH}$ radical (ketyl) and reduce Ag^+ to Ag^0 (Scheme 2.11).

The bimodal behavior in the fluorescence of denatured HSA can be explained by the formation of protein corona arrangements [224] that at silver nanoparticle concentrations lower than 0.38 nM leads to a marked emission enhancement as they locate in the plasmon enhancement region. This enhanced emission becomes a smaller fraction of the total emission as the concentration of AgNP increases due to the finite availability of nanoparticle surface. Effectively, the ratio of HSA/AgNP at the maximum enhancement is close to 160,000 molecules per AgNP, while at AgNP concentrations >0.5 nM this will be less than 16,000 molecules per AgNP. These data are fully compatible with the formation of corona arrangement where there is a considerable excess of “free protein” in the aqueous phase. This corona arrangement is obviously different from the one formed for the native protein since no effect on the fluorescence emission was observed for the non-denatured protein; the changes for denatured HSA, while modest ($\sim 20\%$), are outside error limits and are not observed for the native protein. The most likely explanation is that the formation of an initial shell of the unfolded HSA surrounding the metal surface facilitates the sequential association of more denatured protein.

It was postulated that this protecting effect depends on the number of available NH_2 groups, rather than the macromolecule conformation. These data suggest that electrostatic interactions confer protection to the silver nanoparticle surface [224]. Additionally, it was reported that protein protection against NaCl, and other salts, was not significantly affected by the presence of (≤ 0.5 mM sodium citrate or I-2959). This indicates that these components are not involved in the formation of the corona arrangement. Recognizing that NaCl is not the only substance that can potentially decrease the AgNP stability, we also assessed their stability with different buffers such as phosphate buffer saline (PBS, pH 7.0), glucose supplemented phosphate buffer (Hank’s buffer), Dulbecco’s minimum media (DMEM) buffer, MES (2-(*N*-morpholino)ethanesulfonic acid) buffer (pH 7.0), and Tris–HCl buffer (pH 7.0). Results show that even at low protein concentrations, AgNP becomes

stable in all the buffers assessed, with a concomitant PBS redshift of ~ 8.0 nm. Remarkably, as the buffer complexity increases, the protein protection efficacy seems to decrease. In particular, the minimum protein concentration needed for conferring protection to AgNP becomes greater as the number of components in the buffer increases (DMEM > Hank's buffer > PBS). The most noteworthy difference within the buffers was found in the 18-h stability experiments for DMEM, where AgNP PBS clearly decreases after only 3 h, probably due to protein oxidation promoted by the components in the medium (amino acids, vitamins, minerals, etc.). Protein protection was also observed for AgNP in Tris-HCl buffer and to a lesser extent if MES buffer is employed [222].

The effectiveness of native HSA as a stabilizer for silver nanoparticles was also demonstrated by the changes in the PBS absorption upon protein addition. The redshift of PBS in the presence of HSA is a clear indication of dielectric constant changes at the nanoparticle surface. Further, AgNPs are unstable in the presence of chloride ions. Surprisingly, it was found that even relatively low concentrations of HSA can protect AgNP@citrate from different salts/ions such as NaCl or common buffers. Nevertheless, long-term stability for AgNP conferred by HSA is apparently controlled by the medium complexity where an increase in the number of components in the buffer causes the particles to be less stable. Silver nanoparticles can be readily prepared in aqueous solutions under mild conditions using a photochemical method with HSA as protecting agent. The protein is more than just a mere protecting agent, since it could also complex Ag^+ ions and affect the ratio of Ag^+ between the aqueous solution and the macromolecule structure as HSA shows a remarkable affinity for silver ions. Long-term stability experiments have shown that amine-blocked HSA is far less stable than when using native HSA or even the protein alone. The hydrodynamic size measurements for the nanoparticles showed that the nanocomposite size is highly modified when the NH_2 groups in HSA are blocked. It is also of note that when NH_2 -blocked HSA is employed as a stabilizer, in the presence of other AgNP shapes (primarily cubes and plates) and sizes (5–15 nm), these are different from those obtained using native HSA.

Ganeshkumar et al. have exploited the reducing, stabilizing, and biocompatible nature of a biopolymer, pullulan (PI), for the synthesis of gold nanoparticles (PIAuNPs or Au@PINPs, pullulan-covered gold nanoparticle core) [225]. PIAuNPs allowed the attachment of a large number of small molecules. AuNPs were formed during microwaving only. The λ_{max} of PIAuNPs remained at 525 nm before and after autoclaving indicating that PIAuNPs were stable even after autoclaving. The stability of PIAuNPs at various temperatures was checked and found to be stable at all the temperatures, which was also confirmed by visible spectroscopy by taking SPR. The peak appeared at 525 nm confirmed the formation of gold nanoparticles. The zeta potential of PIAuNPs, AuNP@5-Fu (5-Fluorouracil, and 5-Fu) was measured by dynamic light scattering method, showed ~ -27.6 mV, respectively. PCS method was used to confirm the mean particle size of PIAuNPs and it was observed to be ~ 71 nm. PCS measurements yield a significantly larger average gold nanoparticles diameter (~ 71 nm) than the TEM analysis (~ 20 nm); TEM visualizes the dried gold nanoparticles core of the particles, whereas PCS measures

their hydrodynamic diameter in liquid medium, which can be enhanced by hydrophilic pullulan coated on the gold nanoparticles surface.

Chitosan (CHI) acts as a soft template for the formation of multibranched magnetic nanoparticles, and gold coating process was carried out in the presence of chitosan to give better particle dispersity and to avoid agglomeration problems (Chart 2.1). Chitosan is a linear polysaccharide consisting of β -(1 $\rightarrow$ 4)-linked 2-amino-2- deoxy-D-glucose residues, originating from deacetylated derivative of chitin, which is the second most abundant polysaccharide in nature after cellulose. It was nontoxic, biodegradable, biofunctional, and biocompatible. In addition, the main advantage of chitosan matrix is to act as stabilizing agent in the formation of nanoparticles due the presence of hydroxyl and primary amino groups. The stabilizing agent used in chitosan and the addition of gold chloride salt solution to a mixture of water lead to the formation of a complex containing both chitosan primary amino group and gold (III) which appeared as an orange color solution. At room temperature, chitosan-based reduction kinetics is low, and Au^{3+} ions were complexed on the surface of chitosan; after the addition of ascorbic acid to this solution, the dark orange color of solution is turned to the clear solution due to the reduction of Au^{3+} into Au^0 ions in chitosan matrix [131].

In the presence of chitosan, the sequential addition of ascorbic acid, HAuCl_4 , and seed as $\text{Fe}_3\text{O}_4@\text{Au}$ gave the anisotropic-shaped nanostructure. Indeed, it was reported that the role of Ag^+ is to assist the anisotropic growth of gold branches on certain crystallographic facets (Scheme 2.12) [226]. The directed surface growth and the particle dimension are also related to the presence of silver ions in the

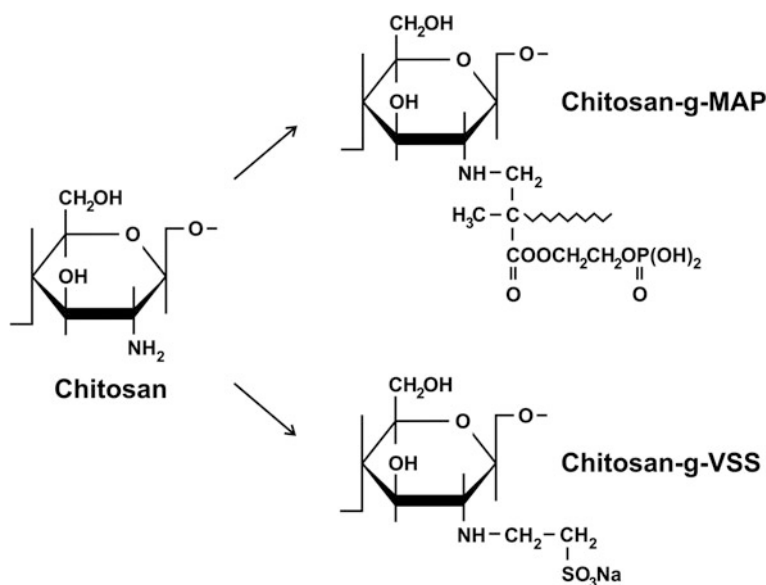
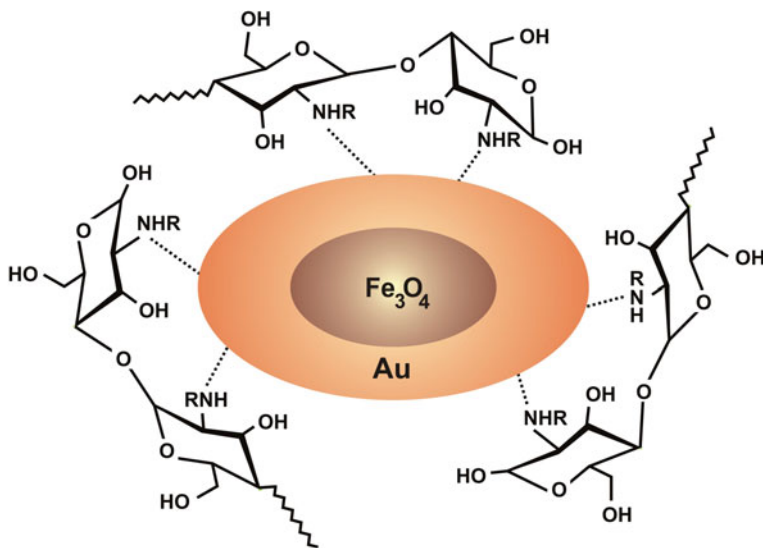


Chart 2.1 Chitosan-type templates

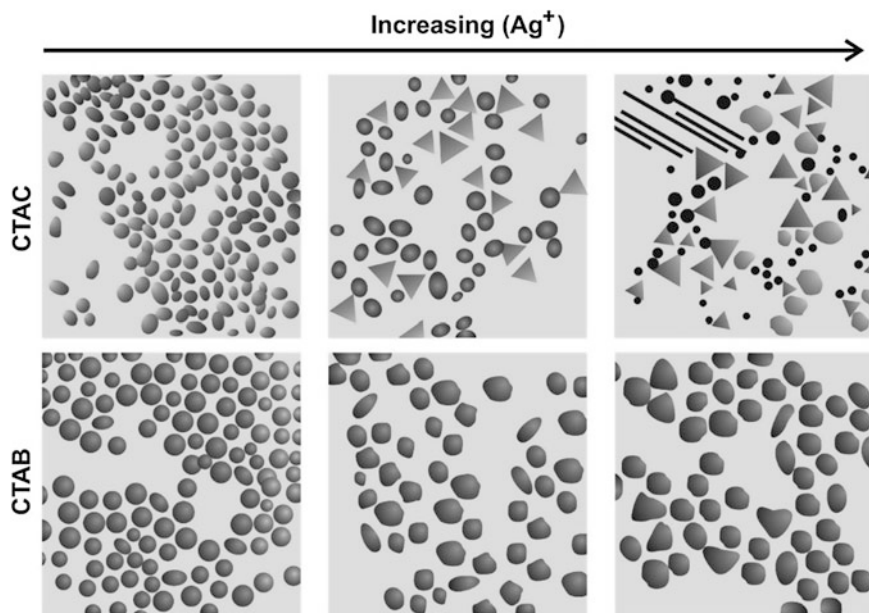
growth solutions. The presence of Ag^+ is necessary for branched nanocrystal formation. In the absence of silver ion in growth solution, the observed extinction spectrum is characterized by a plasmon resonance band around 550 nm of gold layer since in other study, the wide plasmon resonance band of gold layer is located at approximately 800 nm. This redshift is due to the increase of surface area of the magnetic nanoparticles. Plasmonic metallic nanoparticles are characterized by the presence of localized surface plasmon resonance, and this plasmon field is generated on the surface of the nanoparticles, which enhances both absorption and scattering. For nanoparticles of similar shapes, a redshift of the LSPR peak is observed as the nanoparticle size is increased [227].

Additives such as surfactants (e.g., CTAB, sodium dodecyl sulfate) [167, 228], polymers (e.g., PVP, PVPO, PVA, ...) [229], foreign ions (e.g., Ag^+ , Cu^{2+} , Cl^- , Br^- , I^-) [230, 231], ligands (e.g., inorganic ions, thiols, amines ...) [232], and impurities [230] present in the reaction medium have been already partly discussed to play important roles in controlling the morphology of particles produced. Surfactants, ligands, or polymers were commonly added as stabilizers to impart stability to nanoparticles against aggregation, since colloidal particles tend to aggregate to decrease the overall surface area and energy. Later these species were used during synthesis as growth-arresting agents to control the particle size, morphology, and surface properties. That is why nowadays a general term, capping agent, is used to refer them. Through their interactions with particle surfaces, capping agents can inhibit the incorporation rate of growth units onto the particle surfaces, change the surface free energies of different facets, and, thereby, change relative growth rates of the facets [233].



Scheme 2.12 $\{\text{Fe}_3\text{O}_4@\text{Au}\}@\text{CHI}$ the anisotropic-shaped nanostructure [226]

Nanocrystal growth is a complicated process, and it is the combination of many ingredients that leads to the final shape. CTAB is known as the most suitable reagent to control the formation of AuNPs [234]. It was found that the type of surfactant was critical for the formation of highly anisotropic particles. While triangular nanoprisms could be generated with cetyltrimethylammonium chloride (CTAC), for example, the yield of nanoprisms was lower and the size distribution was broader with CTAC (Scheme 2.13; Fig. 2.5). The use of benzyldimethylhexadecylammonium chloride (BDAC) was particularly important for the formation of nanowires; nanowires were rarely observed in CTAC samples. When BDAC was replaced with CTAB, a mixture of different shapes (spheres, rods, etc.) was formed instead of triangles or wires presumably due to bromide ions interfering with silver underpotential deposition (UPD). Therefore, it is the combination of two unusual ingredients, silver seeds and BDAC, that is responsible for the formation of highly anisotropic nanoparticles reported here. Compared to CTAC and CTAB, which have been commonly used in seed-mediated growth method, BDAC has a greater tendency to crystallize due to the aromatic head group. Therefore, they can act as a more rigid organic template and promote the anisotropic growth of nanoparticles by slowing down the growth of (111) facets. Other factors such as reduction potential of surfactant-metal complexes and the affinity of aromatic groups to metal can also impact the growth of nanoparticles [235].



Scheme 2.13 TEM-like images for CTAC and CTAB—variations of particle size and shape with increasing silver salt concentration [234]

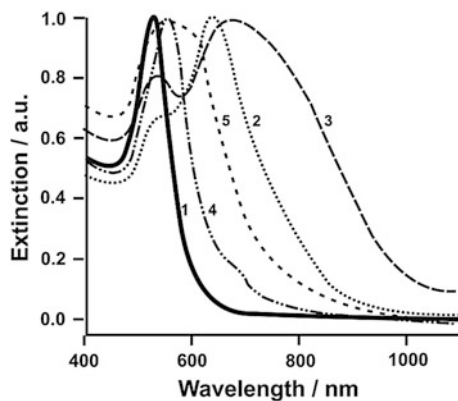
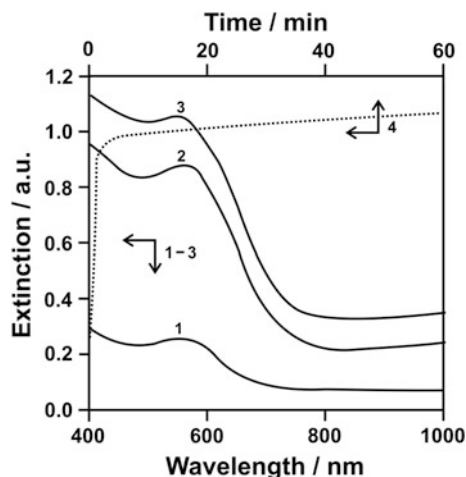


Fig. 2.5 Variations of extinction spectra (CTAC lines 2 and 3, CTAB lines 4 and 5, the black full line (1) is for both systems with the initial silver salt concentration) of nanoparticles synthesized using different surfactants (CTAB and CTAC) with increasing silver salt concentration. BDAC-stabilized silver seeds were used for all syntheses [235]

Fig. 2.6 Extinction spectra showing the growth process for Ag seed particles (1, 2, and 3) and Au seed particles (4, 5, and 6) (*Left panel*). Plot of time-dependent maximum extinction change for the two syntheses shown in (AgNPs) and (AuNPs) (*Right panel*) [235]



The fast growth kinetics with silver seeds was further verified by the sudden initial jump of the extinction in the UV–Vis spectra (Fig. 2.6, curve 4).

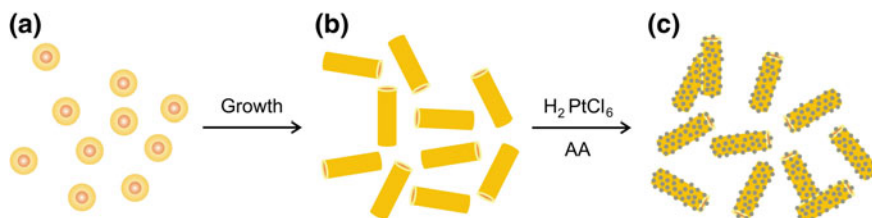
Gold nanorods have been extensively investigated as support, due to their well-established synthesis routes, tunable surface plasmon resonance property, and super catalytical activity. To obtain the dispersed platinum nanostructures, one of the effective routes is to chemically fabricate Pt on preformed nanostructured (nanorods (NRs)) surfaces, to form a core@shell structure. The Au@Pt nanostructure has been synthesized by using gold nanorods as support [236], which can catalyze the oxidation of some organic molecules. The CTAB was also involved in

the synthesis of the core@shell nanostructures in which platinum nanodots (PtNDs) appeared on the surface of seed AuNPs [237]. PtNDs were formed by the reduction of Pt salt (H_2PtCl_6) by ascorbic acid (AA). On the one hand, the CTAB covered the special lattice plane of the AuNRs through a moderate combination of bromide ion with metal; the long hydrocarbon chains of the absorbed CTAB formed a very stable bilayer on the AuNRs, which acted as the directing agents for growing PtNDs on AuNRs (Scheme 2.14). On the other hand, the interaction between the CTAB and Pt surface was significantly weaker, which offered a possibility to control the morphology and preserve the catalytic activity of the PtNDs [238] via a similar approach without using the AuNRs.

Ionic liquids (ILs) are a viable option as stabilizing agents because of their ionic character and can be easily made task-specific as phase-transfer catalysts due to their tunable nature. However, ILs are generally used as temporary stabilizing agents. They are used to halt aggregation of Au(0) produced in the reduction of HAuCl_4 , thus limiting the size of the gold aggregates that form nanoparticles [239]. Several studies have reported the synthesis of transition metal nanoparticles using ILs as the media and stabilizers [240]. The earliest mention in the literature of an IL with a nitrogen cation used as the capping agent for AuNPs was an imidazolium-based cation IL reported by Itoh et al. [241]. Several other imidazolium ILs followed, however, these ILs contained sulfur functional groups which provided permanent covalent stabilization of the gold; these were effectively task-specific ILs that combined the phase-transfer catalyst and permanent stabilizer into one molecule by functionalizing the IL with an aurophilic capping agent (sulfur) [242].

Room-temperature ionic liquids are attracting much interest in many fields of chemistry and industry, due to their potential as a “green” recyclable alternative to the traditional organic solvents. They are nonvolatile and provide an ultimately polar environment for chemical synthesis. Some ionic liquids are immiscible with water and organic solvents, giving biphasic ionic liquid systems, which enables easy extraction of products from the ionic liquid. The miscibility with organic solvents or water is mostly dependent on the appropriate anions.

The ionic liquids based on the imidazolium cation are broadly used for the synthesis of gold nanoparticles [243]. Hydrophilic and hydrophobic properties will



Scheme 2.14 Illustration of preparation processes of AuNR@PtNDs structures, AuNPs (a), AuNRs (b) and AuNR@PtNDs-HD (c) [237]

be tuned by anion exchange of the ionic liquid moiety. The use of the aggregation-induced color changes the gold nanoparticles in aqueous solutions as an optical sensor for anions via anion exchange of the ionic liquid moiety. Among various known ionic liquids, ionic liquids containing imidazolium cation and PF_6^- have a particularly useful set of properties, being virtually insoluble in water. Such biphasic ionic liquid systems have been used to enable simple extraction of products. The transfer of the gold nanoparticles across a phase boundary (water to ionic liquid) via the anion exchange of the ionic liquid by addition of HPF_6 to an aqueous solution of the 1-modified gold nanoparticles was investigated. When HPF_6 was added to the aqueous solution containing the 1-modified gold nanoparticles with stirring, the ionic liquid phase (1-methyl-3-hexylimidazolium hexafluorophosphate) quickly became colored, drawing from the original deep red color of the aqueous nanoparticle solution. The complete phase transfer of the gold nanoparticles was achieved. Before addition of HPF_6 , the surface plasmon absorbance of the gold nanoparticles was observed around 526 nm. In contrast, the absorption disappeared completely after addition of HPF_6 . The transferred nanoparticles displayed no signs of degradation or aggregation. Herein, HPF_6 acts as an efficient phase-transfer agent for the 1-modified gold nanoparticles and allows their solubilization in the ionic liquid phase through the solubility change by the anion exchange from Cl^- to PF_6^- [241].

A one-pot green process is based on the reduction of gold salts in the presence of surfactant, organic polymer and IL, etc. [244], which regulate the shape and size of nanomaterials and avoid their aggregation or precipitation. For instance, Li et al. used microwave to heat HAuCl_4 in IL (1-butyl-3-methylimidazolium tetrafluoroborate, $[\text{BMIM}][\text{BF}_4]$) to prepare gold nanosheet [245], and IL was thought to act as the structure-directing agent. Zhu et al. [246] prepared anisotropic gold nanoparticles by photochemical reduction of HAuCl_4 in $[\text{BMIM}][\text{BF}_4]$ and pointed out that IL was the critical factor for the formation of anisotropic shape. Tsuda et al. fabricated anisotropic gold nanoparticles in bis(trifluoromethanesulfonyl)amide anion-based IL using accelerated electron beam irradiation and γ -ray [247]. These methods are free of additional capping agents, but the reaction conditions are relatively severe. Later, Yang et al. prepared gold networks@IL ($[\text{BMIM}][\text{BF}_4]$) by directly reducing HAuCl_4 with sodium citrate in $[\text{BMIM}][\text{BF}_4]$ aqueous solution [248]. Similar technologies such as photochemical reduction [249], atmospheric plasma [250], and laser irradiation [251] were also utilized to prepare AuNPs using chitosan as the structure-directing agent. In these cases, CHIT was proved to act as a template agent for the formation of anisotropic shape. However, the density of AuNPs obtained was low [249, 250] comparing with physical reduction, the chemical method was easy to achieve under simple conditions. For instance, Carlo et al. used organic acids to reduce HAuCl_4 in CHIT aqueous solution, and the obtained solution was coated on electrode surface to form CHIT–AuNP hybrid film [252]. However, the layout of AuNP on electrode surface is agglomerate.

Yang et al. [253] have utilized IL and chitosan to regulate the formation of anisotropic gold nanoparticle and the shape of hybrid films. As can be seen, the graphene oxide (GO)-modified glassy carbon electrode (GCE) exhibits wrinkled structure. When the reaction is carried out in CHIT solution, the obtained film is stacked on GO/GCE. When both IL and CHIT are present, the obtained hybrid film is similar to that without IL. But with the concentration of IL, increasing the hybrid film tends to roll out. The result indicates that the concentration of IL can influence the morphology of hybrid film. IL acts as a capping agent that is selectively adsorbed on a specific crystal surface of AuNP. At the same time, CHIT, with a large number of amino and hydroxyl groups, enables the simultaneous synthesis and surface modification of AuNP in one pot. Importantly, when the hybrid film is dried on GO/GCE, the CHIT is easy to dry and shrink to form agglomerated and stacked shape. On the contrary, IL is difficult to dry and it can prevent the shrink of CHIT. Therefore, the morphology of hybrid film should be related to the interaction of AuNP, IL, and CHIT. The preparation method can overcome the agglomeration of the dropping mixture and produce three-dimensional and mountain-like shape. Thus, the hybrid film shows larger surface area than the agglomerated and the smooth one.

When the hybrid film is prepared with low concentration of HAuCl_4 , the diameters of AuNPs are about 50–70 nm and AuNPs are sparse. When the concentration of HAuCl_4 increases (i.e., 3 mmol dm^{-3}), the diameters of AuNPs become smaller (about 40–50 nm), the density of AuNP become higher. When the concentration of HAuCl_4 is 4 mmol dm^{-3} , the diameters of AuNPs are about 5–30 nm, the density of AuNP is high, and the layout of AuNP is compact. Comparing with other hybrid film reported [254], the small and dense AuNP-decorated hybrid film is easy to be obtained. The AuNPs are spherical and their diameters are about 30 nm when the reaction is completed in water. When the reaction is performed in CHIT aqueous solution, anisotropic AuNPs are obtained, and the diameters are 30–50 nm, indicating that CHIT is a critical factor to make AuNP to form an anisotropic structure. When the reaction is performed in CHIT–IL aqueous solution, the diameters of major nanoparticles are 5–30 nm, which means that IL plays an important role to control the diameter of AuNP [253].

Furthermore, it has been observed that foreign ions (metal, halides, etc.) play important roles in the morphology control of the NMNPs [230, 255]. They generally adsorb on a certain set of facets of the growing particle more strongly than others. Such preferential adsorption affects the growth rate of a particle in an anisotropic fashion or may influence the formation of defect structure of the seeds, resulting in the modification of the final crystal shape [255]. However, the actual roles of most of these additives or impurities in morphology control are neither clearly understood nor always recognized. For instance, two schools of thought (viz., soft template and preferential-surface adsorption) exist regarding the roles of surfactant (or their mixtures) in the silver- and gold-nanorod formations [218, 256]. It is worth pointing out here that the impurities present in many chemical reagents can play a vital role in controlling the shape of the nanoparticles. For example, Smith and Korgel recently reported that the yield of gold nanorods varied strongly

depending on the different batches of CTAB obtained from different manufacturers [257]. Millstone et al. also reported a similar observation [230]. They claimed that CTAB, depending upon the supplier, has an iodide contaminant, which acts as a key shape-directing element. One should be careful about the changing behavior of the additives under different reaction conditions (e.g., temperature) [258]. For example, Miyazaki and Nakano reported that the temperature-dependent conformation change of poly(*N*-isopropylacrylamide) affected the shape of platinum nanoparticles formed upon the reduction of K_2PtCl_4 by hydrogen [259]. Nature of solvent may also be important in the control of nanoparticle morphology. Later, Gao et al. found that in the presence of the same capping agent, PVPo, the formation of gold crystals with {111} facets was more favorable, which changed to the {100}-type in ethylene glycol [260].

Since the very first SERS investigations in silver hydrosols, a lot of interest arose about the influence of the addition of halide anions on SERS spectra. For most of the adsorbed molecules, an increase of 2 or 3 orders of magnitude of the SERS signal is observed upon addition of the halide anions to silver colloids. It is necessary, however, that halide anions are specifically adsorbed on silver particles and this generally occurs for chloride, bromide, and iodide anions. Later, this “activation” effect has been thoroughly investigated, because single-molecule SERS signals have been only detected in the case of activated silver colloids. Several explanations of the SERS activation due to the addition of halide anions were proposed, essentially based on the formation of Ag^+ -halide-ligand surface complexes with a large charge transfer between adsorbate and metal or on the increase of the local electromagnetic field by aggregation of metal colloidal particles. Moreover, it is of note that both the adsorption mechanism and the surface coverage of an organic ligand are strongly affected by the addition of halide anions. This could explain why the SERS spectra of some adsorbates are markedly enhanced by the addition of halide anions [261], whereas others are negatively affected by it [262]. The silver colloid activation is still a controversial point. Aggregation of the silver and gold nanoparticles upon addition of halide anions has been observed by microscopic and UV-Vis absorption measurements. However, no significant increase in the SERS enhancement of 1,2,3-triazole (hereafter TZ3) has been detected in both silver and gold hydrosols by addition of chloride or bromide anions, as, instead, expected on the basis of the electromagnetic mechanism after colloidal aggregation [263]. In the case of gold hydrosols at their usual pH (6), no difference is observed between the SERS spectra with or without halide addition. In the case of silver and basified gold colloids, instead, the presence of coadsorbed halide anions induces the adsorption of TZ3 as neutral molecule through one nitrogen atom. The occurrence of several bands in the SERS spectra of TZ3 adsorbed on Ag/halide or Au/halide colloids is due to the adsorption of both tautomers of TZ3, as deduced by the spectral and computational results [264].

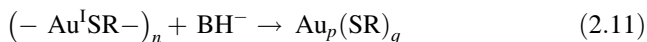
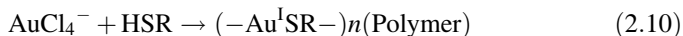
Ethanol as well as water was suggested to act as very weak reducer agents [87]. Thus, tetrachloroauric acid was mildly stirred in ethanol at 35 °C for a couple of days, but no changes in the color were observed. However, as the temperature was increased to 68 °C the color changed immediately from yellow pale to pink,

indicating that the gold salt was completely reduced and the atoms nucleated forming small gold nanoparticles. Therefore, considering that the synthesis was carried out at temperature lower than 45 °C, the ethanol can also be discarded as reductant at the working temperature. In a similar experiment, HAuCl_4 was mildly stirred in water at 35 °C for one day. Unlike what happens with ethanol, smooth changes in color were observed after one day, indicating that water is a weak reductant at the working temperature.

Most of the methods used to produce gold nanoparticles involve the reduction of Au(III) using strong reducing agents such as NaBH_4 which generates gold nanoparticles very rapidly [110, 265]. The introduction of strong capping agents during nanoparticle synthesis has the effect of stopping the growth of the NPs whereas weakly associated ligands allow for continued growth [266]. As a result, the presence of the capping agent whether strongly or weakly binding is essential during the nanoparticle synthesis in order to control the nanoparticle size and shape and to prevent aggregation. However, use of strong capping agents makes further surface modification with alternative ligands challenging [267]. In addition, the sizes of the nanoparticles produced using strong capping agents, e.g., alkylthiols, vary from batch to batch [268]. In order to synthesize AuNPs without the use of strong capping agents, the synthetic method requires a reducing agent to generate nanoparticles at a slow rate with the resulting particles stabilized by coordinating ions or ligands which are already present in the reaction mixture from the gold salt precursor.

Ligand exchange reactions have proven a particularly powerful approach to incorporate functionality in the ligand shell of thiol-stabilized nanoparticles and are widely used to produce organic- and water-soluble nanoparticles with various core sizes and functional groups. However, this approach continues to be limited by a number of challenges, including difficulties incorporating charged ligands into the ligand shell, controlling the core size independent of the ligand used, and driving complete replacement of the original ligand shell. Direct synthesis approaches have also been employed to prepare functionalized nanoparticles but most of these methods suffer from the incompatibility of functionalized ligands with the reaction conditions and show a strong dependence of the core size on the stabilizing ligand used during synthesis [269]. This novel approach has been developed for the preparation of diverse libraries of ligand-stabilized metal nanoparticles that address the challenges stated above. It consists of a straightforward two-step procedure, involving (i) preparation of well-defined phosphine-stabilized precursor particles (d_{CORE}) and (ii) functionalization of these particles through ligand exchange reactions with functionalized thiols. The small set of thiols previously used in this approach suggested that the method might be extended to provide general, convenient access to functionalized, thiol-stabilized gold nanoparticles with a controlled core size. The studies mainly explore the dynamics of ligand exchange reactions between thiol-stabilized gold nanoparticles and other thiols [270]. The results demonstrated that different thiol molecules have different reactivity for bonding with gold in the formation of the nanoparticles. Possible causes for the reactivity difference include (1) difference in the electron density of sulfur atom (–

S[−]) and (2) presence or absence of a metal chelation effect. The electron-withdrawing carbonyl group (−C=O) in tiopronin (for example) makes its sulfur atom less electron dense compared with the sulfur in EG₃-SH. According to the nanoparticle formation mechanism proposed by Shiffrin et al. [18], as shown in Eqs. 2.10 and 2.11, the more electron-rich thiol group (HS[−]) in EG₃-SH reacts faster with AuCl₄[−] in the polymer formation step. After the polymer was reduced by BH₄[−], the nanoparticle surface is bound more favorably to EG₃-SH. In addition, the tiopronin molecule has an acid group (−COOH) that could chelate to Au³⁺ metal salt to prevent the formation of Au(I)−S−R, resulting in low reactivity [271]:

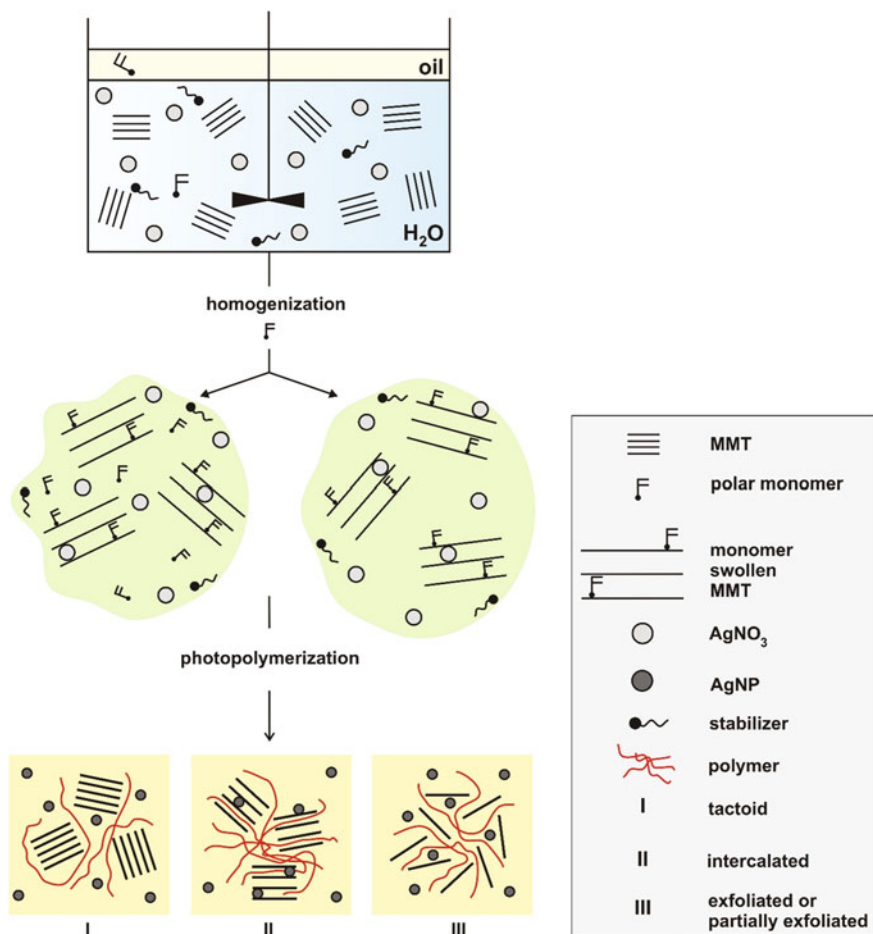


Graphene oxide (GO), a derivative of graphene, is obtained through the intense oxidation of natural graphite [272]. Since GO sheets have large surface areas and the edges are covered with epoxy, hydroxyl, and carboxyl groups, GO has many potential applications, such as adsorption [273], the separation of pollutants [274], and catalytic supports for chemical reactions [275, 276]. Its structure also endows GO with the ability to be functionalized. GO is viewed as an amphiphile with a largely hydrophobic basal plane and hydrophilic edges, which make it behave like a colloidal surfactant [277]. GO has been used as a functional surfactant in a Pickering emulsion polymerization to fabricate a poly(methyl methacrylate)/GO composite [278]. The method is a soap-free environmentally benign process that produces high-quality polymer graphene composites. The GO sheets are both hydrophilic and hydrophobic due to the basal planes of the carbon networks and oxygen-containing functional groups on those planes. With the amphiphaticity, GO sheets act like a functional surfactant and can participate in Pickering emulsions as the stabilizer [279]. Similarly, Pickering emulsion can be also stabilized by AuNP/GO [280].

To obtain metal nanoparticle composites through the efficient, convenient, and easy way, Liu et al. have developed a one-step approach based on the interfacial thiol−ene photopolymerization, in which microcapsules (MCs) and metal nanoparticles are generated simultaneously by irradiation of ultraviolet (UV) light [281]. The in situ photoreduction of metal ions can minimize the number of processing steps in fabrication of metal nanoparticles [282]. Using thiol groups containing POSS (PTPS) as a reactive surfactant, Li et al. recently fabricated the uniform-sized microcapsules through the one-step toluene/water interfacial thiol−ene photopolymerization [283]. This emulsion-based approach is very appealing for the large-scale fabrication of microcapsules. Through adding a metal precursor into the water phase, this approach can be successfully modified to prepare MC@NMNPs. In the presence of amphiphilic polyhedral oligomeric silsesquioxane (POSS) containing thiol groups (PTPS) as a reactive surfactant and trimethylolpropane triacrylate (TMPTA) as a cross-linker, the oil phase of toluene dissolved with a photoinitiator was emulsified into a water phase containing a metal precursor to form an oil-in-water (o/w) emulsion. Upon irradiation of ultraviolet (UV) light,

the thiol–ene photopolymerization and photoreduction at the interface of toluene/water lead to the formation of the cross-linked wall and metal nanoparticles, respectively. A series of gold, silver, and platinum nanoparticle-decorated microcapsules (MC@AuNPs, MC@AgNPs, and MC@PtNPs) were prepared through this one-step interfacial thiol–ene photopolymerization.

Montmorillonite (MMT) is a multilayered material consisting of many parallel arrays of broken plates [284], and the nanomaterials exhibited similar morphologies upon silver functionalization [Scheme 2.15 and Chap. 5 (Scheme 5.2)]. With increased AgNO_3 ratio on MMT, the surface becomes shiny due to the presence of AgNPs and homogeneous fraction surface was detected during the synthetic processes; AgNO_3 is intercalated into the gallery regions of montmorillonite/polymer and formed hybrid framework. It can also be seen that the AgNPs@MMT and/or MMT@AgNPs nanocomposites exhibited card-like and ball-like homogeneous



Scheme 2.15 The mechanistic routes of clay (montmorillonite, MMT) polymer–nanocomposites formation in the thermally- and photoinduced reduction of silver salts

surface fractions and form one-phase morphology. The HRTEM images revealed that the AgNPs are well dispersed on both MMT surface and pores, and the dark region is increased with increasing silver content, which is in good agreement with XRD analysis [179].

Typical XRD peaks for all samples of trioctahedral subgroup of 2:1 phyllosilicates are observed, which are ascribed to (110), (020), (004), (130), (200), (330), and (060) diffractions. The results indicate that the crystalline structure of the clay sheets had not been destroyed after preparation processes, with observed low intensities peak closely matching those of pure silver (reflections at 38.36° , 44.49° , 64.81° , 77.71° , and 81.81°). The silver-peak (111) is indicating that the silver grains were oriented along the [111] direction, where (111) plane corresponds to the cubic system in the thin films' growth [285]. Despite the intensities of reflections corresponding to the planes in different samples are low, the 5% AgNP@MMT sample shows more reflection intensity indicates more crystallites corresponding to the (111) plane of cubic Ag ($a = 0.4132$ nm). Indeed, the reflection peaks of AgNPs have low intensities owing to their high dispersion on the inner surface of MMT, which is consistent with other report [286]. The crystal grain size was estimated from the full width at half maximum of the Ag (111) peak using the Scherrer equation. The crystallite size for 1, 3, and 5% Ag in AgNP@MMT nanocomposite samples is found to be in the range of ~ 7.4 , ~ 10.7 , and ~ 19 nm, respectively.

MMT is porous material and according to [286], the low intensity of some metal in the porous structure resulted from high diffusion of this metal inside pores. The degree AgNPs dispersion on MMT surface is a function of color intensity and its homogeneity. However, more congregating of the silver nanoparticles is inhibited due to the paraformaldehyde (polyoxymethylene) molecule escaping on the surfaces of the silver particles, then forming a steric hindrance to prevent them from aggregation [287]. Compared to AgNPs [288], MMT@AgNPs exhibit a redshifted peak at 421, 433, and 442 nm for 1, 3, and 5 MMT@AgNPs nanocomposites, respectively. This redshift in the absorption spectra reflects a decrease band gap of the semiconductor, which arises from the size quantization effect, and may be caused by the MMT shell [289]. It was reported that the absorption bands correspond to silver nanoparticles smaller than 15 nm were detected at around 404–415 nm [290]. The symmetric absorption peaks indicate surface plasmon resonance of uniform spherical silver nanoparticles [291]. This implies that when the concentration of silver ions was increased, the size increased. This could be due to different nucleation mechanisms operating at lower and higher Ag^+ concentrations attached to MMT at constant ratio of stabilizing agent.

The corresponding findings for traditionally studied ensembles of palladium nanoparticles includes lowering of the critical temperature for separation of the α - and β -phases with decreasing particle size [292], narrowing of the two-phase region [293], decreasing absorption–desorption hysteresis, increasing slope of the plateau of the corresponding loop [294], and apparent compensation for the influence of surface tension by absorption at subsurface sites [295]. The influence of the particle size/shape distribution on these findings is, however, not fully clear [296]. Other frequent complicating factors are different types of surfactants, polymeric

stabilizers, or strong interactions with the support/host matrix that may affect lattice strain and its relaxation during hydrogenation [297].

With the development of nanoplasmonic sensing, it recently became possible to advance from studies of confinement effects in Pd thin films and arrays/ensembles of Pd nanoparticles to the investigation of hydrogen sorption at the single-nanoparticle level, eliminating ensemble-averaging artifacts [140]. However, these initial single-particle studies did not provide deeper insight into the corresponding physics. The first detailed single-particle experiments were performed by Baldi et al. with individual Pd nanocubes at low pressure and temperature by means of electron energy loss spectroscopy [298]. Instead of a slope in the plateau region observed earlier at the ensemble level for Pd nanocubes by Bardhan et al. [299], they found a sharp phase transition and a size-dependent absorption plateau pressure (the thermodynamics was not quantified). This was explained by a model assuming phase coherence and tensile strain in the particle core, induced by a thin 1-nm subsurface hydride layer, which mediates the phase transition [298]. In contrast, the treatment by Bardhan et al. invoked a thermal-fluctuation-mediated phase transition to explain the observed size-dependent thermodynamic parameters [299].

Syrenova et al. have applied noninvasive single-particle plasmonic nanospectroscopy for the comprehensive experimental assessment of both hydrogenation thermodynamics and hysteresis in individual, surfactant-free, palladium nanocrystals over an unprecedented size (from 17 nm to over 100 nm) and shape range (single-crystalline nanocubes, nano-octahedra, and twinned nanorods) [300]. They rely on wet-chemically synthesized Pd–Au heterodimers, created by electrostatic self-assembly of plasmonic gold nanoantennas and shape-selected Pd nanocrystals we have introduced earlier [301]. Hydrogen sorption is tracked by measuring the spectral shifts of the plasmonic scattering peak of individual dimers, which is proportional to the hydrogen concentration in a Pd particle [302] as here also confirmed specifically by finite-difference time-domain (FDTD) simulations for the three investigated Pd nanoparticle shapes. Plasmonic nanospectroscopy is effective for probing individual functional nanoparticles in situ and in eliminating ensemble averaging to unearth single-particle-specific effects. Here, the authors have employed this approach to investigate in detail the thermodynamics of the hydride formation, and to analyze the hysteresis in the metal-to-hydride phase transition in individual Pd nanocrystals with different sizes and shapes. It was found that hydride formation enthalpy and entropy in the considered size range are nearly independent of particle size or shape. This result is in agreement with the general understanding that particle sizes below 10 nm are required to significantly reduce ΔH [303]. They also observed a sharp hydride phase transition with flat plateaux and with hysteresis (much) wider than for single- and polycrystalline bulk Pd, thin-film, and polycrystalline nanoparticle systems. Moreover, they reported an asymmetric size dependence of the hysteresis through decreasing absorption plateau pressures for decreasing particle size (in agreement with Baldi et al. [298]). At the same time, they found that desorption plateau pressures are constant for all investigated particle sizes and shapes, and in excellent agreement with bulk Pd data. These findings were

explained within the established picture of a first-order phase transition, and the energetic interplay between dislocation formation and coherency strain at the metal–hydride interface during hydride formation. Finally, direct comparison between ensemble and single-particle measurements clearly reveals for the first time that the typical slope on equilibrium plateaux observed for nanoparticle ensembles is not only due to inhomogeneous particle size (as commonly put forward), but also a direct consequences of the specific defect structure of the individual particles—that is, the availability of dislocations to accommodate lattice strain. The latter becomes clear from the fact that nanocrystals with nominally identical size can exhibit hysteresis with widely varying width.

2.2.1 Particle Nucleation and Growth

The understanding and control of crystal (particle) growth are critical to modern nanoscience and nanotechnology [304]. A general strategy for producing high-quality crystals is to maintain the growth solution slightly supersaturated in the atomic or molecular species to be deposited so that the lowest energy equilibrium positions can be attained. Often modifiers (e.g., surfactants) are added to moderate the growth rate or influence the final crystal habit. Growth of gold nanocrystals in solution also relies on surfactants to control unwanted cluster aggregation during chemical reduction of ionic precursors or thermal decomposition of metalorganics. In the case of chemical reduction of a metal salt, for example, the nucleation event may be localized uniformly in space and time by the presence of nanometer size cavities or by creating a microheterogeneous solution. The latter strategy is the basis for nanocrystal growth in the interior of surfactant aggregates (micelles or vesicles). In both cases, the diffusion of new material and its deposition onto the seed nuclei will be much slower than would occur in a continuous phase such as a liquid or gas. In the latter case, the aggregation kinetics as described by the Smoluchowski equation predicts a power law (or log-normal) size distribution in the final product. Such strong polydispersity is generally unwanted. In the case of slow, controlled growth of small nanocrystals in a microheterogeneous environment, one anticipates that facile surface diffusion of atoms deposited on the initial nuclei may create structures controlled by thermodynamic considerations rather than kinetic ones as in classical colloidal (microemulsion) growth. As the growing clusters undergo diffusion and collisions in the solution, intercluster exchange of atoms may even occur in order to achieve a structure with the most thermodynamically stable structure [305].

Models of particle (crystal) development consider two basic steps: nucleation and growth [306]. The creation of a new phase from a metastable (supersaturated or supercooled) state is nucleation. Nucleation occurs via embryos, or germs, which are small, transient clusters, or some entities approximating it, of the new phase. Continuous fluctuations in the sizes of these clusters occur via the incorporation of additional atoms or molecules and their detachment. Where the incorporation event

becomes overwhelmingly more probable than decay, it may result in an embryo growing large enough to become stable, i.e., the energy barrier for its structural fluctuations becomes sufficiently high and a new moiety with well-defined structure is formed [307]. During the nucleation, two opposing energy factors come into play simultaneously. Creation of (new) surface at the boundaries of a nucleus costs energy. On the other hand, there is an energy release due to creation of a new volume [306]. Depending on the surface-to-volume ratio of a developing particle, the resultant energy varies and, therefore, there will be an energy barrier for nucleation. The energy barrier for homogeneous nucleation (spontaneous and random nucleation occurring throughout the solution) is high and hence requires higher degree of metastability (e.g., supersaturation) compared to heterogeneous nucleation. In the case of heterogeneous nucleation, nucleation occurs on surfaces of preexisting foreign bodies or solid structures; hence, some energy is released by the partial elimination of those preexisting interface. This energy gain diminishes the free-energy barrier and facilitates nucleation. Therefore, heterogeneous nucleation occurs much more often and at the lower saturation level compared to the homogeneous nucleation [307, 308].

In the embryonic stage of the metal nanoparticle nucleation, atoms (formed via reduction of metal precursors) or the combined atom–metal precursor systems assemble to form clusters such as dimers, trimers, tetramers, in solution. These clusters may disassemble or collide with further metal ions/atoms, finally forming an irreversible seed. Nucleation ceases when the concentration of growth units falls below the minimum supersaturation level. Once the seed forms, it acts as a convergence point for growth units (ions/atoms) as long as they are available and grows in dimension. Morphology and growth rate of the seed (which are again functions of thermodynamic and kinetic factors) play major roles in determining the final nanoparticle morphology.

The homogeneous nucleation of nanoparticles is based on the supersaturation of solution by reactants such as precursors, reducing agent, stabilizers, costabilizers, and additives. The increased solubility of component in the continuous phase can be reached by the rising in temperature. The supersaturation state can be then reached by the reduction in temperature. Generation of supersaturation through in situ chemical reactions by converting highly soluble chemicals into less soluble chemicals is a good example of this approach. In a typical homogeneous nucleation synthesis consisting of one step process in which precursor (s), stabilizer(s) and other additives are stirred in the oil- or water-continuous phase and then treated by the heat [309]. The heterogeneous nucleation of metal particles consists of several-step process [310]. In a typical heterogeneous nucleation, the first step is the formation of the primary (seed) metal particles and then the growth of particles is achieved via further steps, for example, by the further addition of precursor(s), stabilizer(s), and additives. Meanwhile, some stabilizers, like sodium dodecyl sulfate [311], sugar ball [312], and polymer (e.g., poly(vinylpyrrolidone)) [313], were used, and some stabilization technologies of thiol-ligand coatings [314] and polymer capping agents [315] were developed to prevent the prepared (sub)nanoparticles from aggregating. At room temperature, citric acid, oxidizable solvents (such

as alcohols or DMF), and polymers (e.g., poly(vinyl alcohol) (PVA), PVPo, PVP, etc.) show weak reducing properties toward most of the metal precursors. However, they are capable of reducing a number of metal ions at elevated temperatures [316–318]. In most of the cases, these reducing agents play simultaneous roles of solvents and stabilizers. Depending on the reduction potentials of the metal precursor and the reducing-agent systems, the temperature required for reduction varies.

In the case of homogeneous nucleation, the shape of a (seed) crystal under equilibrium (thermodynamic) conditions can be predicted on the basis of Gibbs–Wulff theorem. The equilibrium (or Gibbs–Wulff) shape of a crystal is one that minimizes surface energy for a given enclosed volume. If the surface energy is isotropic (as for a liquid), the equilibrium shape will be spherical as the sphere has the minimum surface area for a given volume. In the case of crystalline solids, the surface energy is anisotropic. Therefore, total surface energy is not only determined by the surface area but also by the nature of the surface facets. Therefore, the energy-minimizing shape is obtained by enclosing the crystal with the facets of the lowest possible surface energy as well as truncating the facets in order to give minimum possible surface area for a given volume, which results in a polyhedron shape. For a face-centered-cubic (fcc) crystal structure, the surface energies (γ) of the low-index crystallographic facets are given in the order [307, 319]:

$$\gamma\{111\} < \gamma\{100\} < \gamma\{110\} \quad (2.12)$$

Based on this facet energy, minimum surface-energy requirement predicts that the seed crystals of fcc metals should show a tendency to adopt a tetrahedral or an octahedral shape enclosed by $\{111\}$ facets. But tetrahedron or octahedron shapes are not the minimum area shapes for a given volume. Therefore, the Gibbs–Wulff shape for an fcc crystal structure is a truncated octahedron, which is enclosed by eight hexagonal $\{111\}$ facets and six square $\{100\}$ facets. Though truncation introduces a relatively high-energy $\{100\}$ facet but generates nearly spherical shape, thereby decreasing the total surface area and free energy. At very small (nanometer) sizes, the equilibrium shape is an octahedron, corresponding to the disappearance of the $\{100\}$ facets [320]. The regular polyhedron shapes can be obtained only at 0 K, where the surface-energy anisotropy is maximal. The surface-energy anisotropy decreases at high temperatures and rounded parts appear in the equilibrium shape [321].

In the case of heterogeneous nucleation, the seed can grow in an epitaxial or nonepitaxial way. Epitaxy is the technique of growing a crystal (called deposit or overgrowth), layer-by-layer, on another crystal (substrate). In the epitaxial growth, the deposited metal takes on a lattice structure and orientation identical to those of the substrate. Chemical compositions of the deposit and the substrate may be the same (when it is termed as homoepitaxy, e.g., gold seed to gold nanorod), or different (in the case of heteroepitaxy of the different metals). The deposit and substrate may differ in the nature and strength of their chemical bonds as well as in their lattice structures. The chemical bond between the deposit and substrate determines the degree of interaction that can occur between the two, while the

lattice mismatch determines the spatial variation of the interaction. A strong deposit–substrate interaction and small lattice mismatch stimulate epitaxial growth. According to the Wulff–Kaischew theorem, the equilibrium shape of a supported (macroscopic) crystal is determined not only by the surface energy (γ) of the facets but also by its adhesion energy (β) with the support [320]. Depending on the magnitude of γ as compared to β , various degrees of truncation of epitaxially formed nuclei (as compared to homogeneously formed nuclei) may result. The presence of strain at the interface due to a mismatch (misfit) between the lattice parameters of the support and the deposit crystal may cause deviation from the equilibrium shape. When the crystal structures are the same, the mismatch (m) between the two lattices is defined by [307]

$$m = (a_d - a_s)/a_s \quad (2.13)$$

where a_d and a_s are the lattice parameters of the deposit and the substrate, respectively. For zero mismatch ($m = 0$), edges between the top facet (parallel to the substrate) and the lateral facets (perpendicular) follow a straight line with crystal growth, meaning that the shape is self-similar (the Wulff–Kaischew case). But for nonzero mismatch ($m \neq 0$), the deposit crystal grows faster in height than laterally when the height-to-width aspect ratio is no longer constant and larger aspect ratios (i.e., taller crystal) are obtained with the larger mismatch. The equilibrium shape then deviates from the Wulff–Kaischew case. Qualitatively, as the depositing crystal layer is strained at the interface, it prefers to decrease the interface area and to grow at the top to relax more easily. However, the elastic energy increases with the size of the crystal and at a given size the system will partially relax the strain by introduction of dislocation. In the case of formation of an epitaxial phase, mechanisms of nucleation and overgrowth have been categorized into three types, namely the Frank–van der Merwe mode, the Stranski–Krastanov mode, and the Volmer–Weber mode [322, 323]. These modes have been deduced from equilibrium considerations of the energy balance between the surface energy and the interfacial energy for lattice-matched systems. The Frank–van der Merwe mode, where 2D layer-by-layer growth is observed, occurs under lattice-matched or slightly mismatched conditions with high interfacial bond energies and low supersaturation to suppress 3D nucleation [322, 323]. In Stranski–Krastanov mode, a 2D layer of adsorbed atoms is formed under conditions of undersaturation, which turns into 3D growth under conditions of supersaturation (2D layer followed by 3D islands on top). In the Volmer–Weber mode, which occurs under highly lattice mismatched conditions, 3D nucleation occurs under conditions of supersaturation, followed by growth of 3D islands leading to their coalescence [322, 323].

From crystallography, we know that for crystals grown under surface-control conditions, the mechanism of crystal growth can be determined by the structure of the crystal face. It is known that closely packed flat faces (F-faces) grow more slowly than stepped faces (S-faces) or kinked faces (K-faces). Thus, in a growing crystal, F-facets will be exposed more and more, while S-faces and K-faces will gradually disappear. This results in a shrinkage in area (or elimination) of

higher-energy facets, while the area of lower-energy facets increases [231]. Consequently, in contrast to the unique equilibrium shape (at a given temperature) of a macroscopic crystal, several polyhedral growth shapes, including highly anisotropic ones, can be obtained by fine-tuning the relative growth rates of the different facets. The surface energy of a facet can be modified by the adsorption of various additives.

Mass-transport-limited growth is another source of anisometric development of nanoparticles. If interfacial processes are extremely fast during a crystal growth process, the long-range transport of mass controls the rate of growth. Crystals grown under such far-from-equilibrium (high-supersaturation) conditions often show complex shapes, dendritic or branch formation. Fast interfacial process creates a depletion zone around a crystal at the crystal–solution interface due to fast accommodation of the growth units (atoms, ions, molecules), and the supersaturation increases with distance into the parent phase. When a depletion zone is formed around a crystal with polyhedron shape, the apexes of the crystal protrude into the region of higher concentration [231]. Consequently, the rate of growth of any apex (protrusion) will be greater than the growth rate of the rest of the crystal facets, leading to the formation of branches. The diffusive nature of long-range transport processes gives rise to such morphological instabilities, leading to shapes like dendrites [324]. One can summarize different growth conditions as follows: (i) At or near equilibrium growth conditions, faces with the lowest surface energies dominate the crystal habit. (ii) In crystals grown under surface-control conditions, faces with the slowest growth rate dominate the resulting habit. (iii) For diffusion-controlled continuous growth conditions, the crystal habits tend to be rounded, as all crystal faces are rough and predicted to grow at the same rate. (iv) At very high supersaturations, morphological instability can occur and dendritic, cellular, hopper, etc., growth forms may appear.

In general, colloidal particles in a dispersion medium are subject to Brownian motion, and this produces frequent collisions between particles [325]. During such a collision, there are two basic interactions between the particles that determine their stability: one being the attractive forces (van der Waals attractive forces often dominated by a metallic core) and the other being the repulsive forces (mainly electrostatic and steric hindrance). If the attractive forces dominate, the particles will aggregate; in contrast, if the repulsive forces dominate, the system will remain in a dispersed, stable state. For nanoparticles in solution, due to the van der Waals attractive forces acting continuously between them, it is necessary to introduce a repulsive force to maintain particle stability [326]. For example, gold nanoparticles are commonly synthesized through the reduction of auric acids in water using trisodium citrate, with the citrate ions also serving as stabilizing ligands providing surface-bound negative charges, repulsive electrostatic forces around the gold nanoparticles [327]. Upon the chemisorption of electrostatically neutral small molecules, the molecules displace citrate ions from the AuNP surface, reducing or eliminating the surface charges [328]. Without strong charge–charge repulsions, these monolayer-coated AuNPs can be driven to each other by van der Waals attractions, leading to aggregation. In most cases, aggregation of AuNPs is an

irreversible process, and the presence of irreversibly aggregated AuNPs changes the particle size distribution, optical properties, and the surface-to-volume ratio for the AuNPs in solution, making it difficult or impossible to employ them in various applications [329].

In liquid-phase synthesis of NMNPs, nucleation and growth depend on the nature of the reducing agent and stabilizing ligands, the identity of the metal ion precursor, and reaction temperature [266]. In a typical liquid-phase synthesis, the nanoparticle formation process undergoes three distinct stages as follows: (1) reduction and generation of active nuclei, (2) formation of seed particles upon collision of active nuclei, and (3) formation of larger nanoparticles via a growth process, which may be Ostwald ripening or aggregation. In liquid-phase synthesis of nanoparticles, sodium citrate and sodium borohydride are the most commonly used reducing agents. The synthesis of nanoparticles via the citrate reduction method is generally performed at elevated temperatures (85–100 °C) [19, 330]. However, sodium citrate alters the solution pH due to its weakly basic character and influences nucleation and growth [331], causing conditions under which the nanoparticle formation mechanisms contradictory and uncertain [332]. In the case of sodium borohydride-based synthesis of nanoparticles, nucleation and growth take place on a millisecond timescale [333]. As a result, direct time-resolved measurements are extremely challenging and required special instrumentation [334]. Although real-time TEM (tTEM) techniques have been recently introduced to monitor nanoparticle growth [335], characterization of the early stages of nucleation and growth still remains elusive. In addition to using TEM, mass spectrometry was introduced to investigate the formation of thiolate-stabilized gold nanoparticles [336]. However, this method did not provide information about the nucleation and growth processes during nanoparticle formation. A separate study reported aggregative growth by evaluating precursor decomposition at elevated temperature [337]. However, this method required additional cleaning to purify the nanoparticles for each step of data analysis, which could alter the nanoparticle size distribution adding ambiguity to the proposed nanoparticle formation mechanism. Furthermore, LSPR properties of nanoparticles are strongly dependent on their local dielectric environment [338].

The NMNP growth, thus, is generally categorized by two processes: diffusion-controlled Ostwald ripening and aggregation/coalescence. The diffusion-controlled Ostwald-ripening growth can be differentiated from the aggregative/coalescence growth by three distinct observable characteristics during the nanoparticle formation as follows [266, 339]: (1) The final nanoparticles should be single crystalline in nature (2) the nanoparticle growth kinetics should be nonsigmoidal, and (3) the early reduction process should not involve a bimodal size distribution. It was reported that the evolution of the LSPR peak with time during silver nanoparticle formation was nonsigmoidal. Moreover, it was also found single crystallinity of the final AgNPs and the absence of a bimodal size distribution at the early stage of nanoparticle formation. These data are consistent with diffusion-controlled Ostwald-ripening growth during the slow reduction and formation of AgNPs [340].

The digestive-ripening process contributes to the regulation of the particle growth and particle distribution. The entire process from an as-prepared colloid to a digestively ripened one can be categorized into three steps, namely (1) addition of the ligand to the as-prepared colloid to break the bigger particles into smaller ligand-capped particles (2) isolation of the ligand-capped particles from reaction side products, and (3) refluxing the isolated colloid from step 2 with additional ligand to obtain the digestively ripened colloid. There are two important steps in the above process, which differentiate useful ligands from the rest. In the first step, the ligands (except alkanes) break the big prismatic-shaped as-prepared particles into nearly spherical and relatively monodisperse colloids. The next step involves the isolation of these ligand-stabilized small spherical particles from the reaction side products. Two slightly different protocols were employed for this. In the first one, the ligand-stabilized colloids were precipitated by adding excessive amounts of ethanol or acetone. This worked well for thiol-, amine-, and silane-coated particles. In all the other cases, the ligands were probably not securely attached to the particle surface, leading to the coagulation of particles when ethanol or acetone was added, and they could not be redispersed in toluene. Alternative methods like extracting the side products and surfactants with water were effective for only phosphine-stabilized particles. In all the other cases, shaking with water-formed emulsions and the colloids decomposed rapidly, making them useless for digestive ripening. The successfully isolated colloids were either redispersed in toluene (thiol-, amine-, and silane-capped) or were taken as it is (phosphine); a second dose of ligand was added to them and they were subjected to reflux, resulting in the formation of a nearly monodisperse gold nanoparticles in all the cases [340].

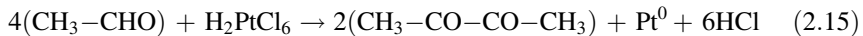
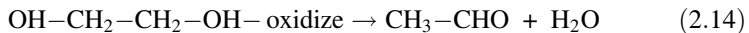
Furthermore, to fully utilize the functional properties of the nanoparticles, well-dispersed systems are desirable. Recently, solvents and the soft templates have been widely used to control the synthesis of metal nanomaterials because their coordination interaction with metal ions provides a good way to control the size and, more importantly, the size distribution of nanocrystals. By changing the reaction conditions, for example, the concentration of starting materials, the nature of the solvents, and the suitable capping/stabilizing agents, it is possible to synthesize a variety of nanocrystallites with different sizes. In the solvothermal process, the capping agent can covalently bind to the surface atoms of the nanocrystallite and can thus prevent them from forming bulk materials. Therefore, solvothermal process has recently been extensively applied to the synthesis and design of nanomaterials of new structures and properties.

Gold nanoparticles show distinct absorption in the visible region due to surface plasmon resonance, and their fundamental optical properties are studied using continuous white light. On another front, pulsed laser light enables us to inject much energy into materials and expand the research field. Studies on ultrafast energy relaxation dynamics in gold nanoparticles induced by femtosecond laser pulses are good examples. Irradiation of intense pulsed laser light to gold nanoparticles induces their size reduction, size enlargement, and morphological

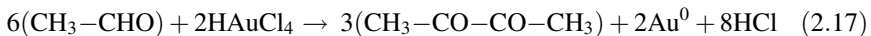
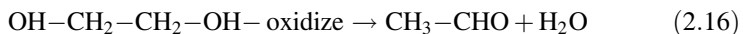
changes [341]. The photothermal process in which the absorbed photon energy heats the particles in a few picoseconds is considered to cause enlargement and morphological changes. Morphological changes of ellipsoidal gold nanoparticles with low aspect ratios to spheres occurred ca. 100 °C lower than the melting point because of surface melting. However, for laser-induced size reduction, two kinetic processes are proposed; one is the vaporization of particles induced by a photothermal process in which particles vaporize at the boiling point [342], and the other is a kind of Coulomb explosion of particles induced by electron ejection from particles. For femtosecond laser irradiation to gold nanorods, experimental results are in contrast with the hypothesis based on the photothermal process since the size reduction of gold nanorods occurred without correlating with the fact that the temperature of the particles reached the boiling point. However, Inasawa et al. [341] suggested a semiquantitative model that explained the maximum diameter of particles, existing in the system after sufficient laser irradiation, reported by Takami et al. [342]. Their model was based on the heat balance, including the heat dissipation from a particle to the surrounding media, because the heat dissipation occurred in 100–200 ps (shorter than the pulse width used by Takami et al.; they used nanosecond laser pulses [342]). Their work supports the photothermal process as its mechanism. In addition to the contrasting experimental results above, phenomenological details, such as to what extent particles reduce their sizes per one pulse and what is the main factor determining the size of small particles, which are generated by laser-induced size reduction, are not yet known. It was revealed that the size reduction of gold nanoparticles under picosecond laser pulses occurred even below the boiling point because of the gold vapor formation around hot liquid gold drops. With sufficient laser energy for the boiling of particles, gold vapor can also be formed inside liquid gold drops, and such bubbles go to the outside of the drops with some volume of liquid gold around the bubbles, resulting in the formation of particles with gold strings on their surfaces. Our results also indicate that the important factor that determines the phenomenon is not temperature but the vapor pressure at the liquid interface [343].

Modifications in temperature influence the reaction by changing the stabilization of the complexes formed between metal precursors and the surface modifiers, e.g., PVPO, and the nucleation rate of the reduced metallic atoms. Characterization of these systems has been a difficult process where researchers have employed indirect measurements to identify the localization of the elements within the nanoparticles. A novel approach to study this kind of particles is based on the use of a high-angle annular dark-field (HAADF) technique, in a TEM, which allows the observation of the interfaces between layers of different elements due to differences in atomic number, densities, or the presence of strain fields due to differences in lattice parameters. This is mainly useful when the structure of the particles is of the core@shell type. On the other hand, it is known that small metallic particles show characteristic absorption bands in the UV-Vis region of the electromagnetic spectrum, but their spectrum can be modified depending on the characteristics of the

suspending medium, composition of the metallic structure, the presence of surfactants or any other surface modifier besides the size of the particle. Reaction proceeds in general as an oxidation of the ethylene glycol reducing the metallic precursor to its zero-valence state:



This is the reaction involved in the reduction of Pt^{4+} to Pt^0



This reaction describes the reduction of Au^{3+} to Au^0 . In the presence of a surface modifier, the reaction changes depending on the ability of the metal to coordinate with it, as in the case of PVPo where the metallic precursor could coordinate with the oxygen of the pyrrolidone group, when the particles are in the nanometer size range, while when they are in the micrometer size range the coordination is mainly with the nitrogen, as reported by Bonet et al. [344].

The analysis of the bimetallic synthesis suggests that at lower temperatures (100 and 110 °C) the gold reduces and nucleates much faster than the platinum and that an interaction between Pt and PVPo is strong enough to prevent the two elements from forming bimetallic structures. However, at 120 °C there seems to be a balance between the reduction and nucleation rates of Pt and Au, considering Pt was given one more minute in the reaction. This is why we observe an interaction between the elements and the formation of bimetallic structures. However, at this temperature there is a combination of a few Au@Pt nanoparticles (particles > 10 nm) with a combination of Pt@Au nanoparticles (particles < 10 nm) and eutectic alloyed nanoparticles. In the temperature range between 130 and 170 °C, Pt@Au particles were obtained. And in the last two temperatures (180 and 190 °C), Pt@Au nanoparticles with thicker Au shells were synthesized, as observed in the HAADF images. In all the temperatures above 110 °C, the presence of eutectic alloyed nanoparticles was also detected [345].

The growth of metals on oxide surfaces is important in numerous technologies including electronic device fabrication and heterogeneous catalysis. With respect to the latter, the activity and selectivity of metal-catalyzed reactions are often sensitive to the metal particle morphology. For example, the catalytic activity of gold supported on certain oxides depends critically on the morphology of the clusters. In general, the morphology of metal particles on oxide surfaces depends to a large extent on defects, particularly point defects such as oxygen vacancies. The research has been addressed to the relationship between metal cluster nucleation/growth on oxide surfaces and defects; however, many questions remain unanswered. Using scanning tunneling microscopy showed that bridging oxygen vacancies on TiO_2 are

active nucleation sites for gold clusters. In addition, this was suggested that the diffusion of a vacancy–cluster complex plays an important role in the formation of larger gold clusters. Using atomic force microscopy, point defects in MgO have been quantified by estimating the Pd cluster density as a function of the deposition surface temperature. In a theoretical study, the binding energies of various metals to MgO have been calculated and showed that dimers of noble metals are more stable at oxygen vacancies. Using STM, preferential decoration of Pd and Rh metal particles on line defects of Al_2O_3 has been discussed. Furthermore, defects in crystalline SiO_2 thin films have been studied using ultraviolet photoelectron spectroscopy (UPS) and metastable impact electron spectroscopy techniques (MIES). On the basis of STM studies, gold nanoclusters can be used to highlight defects in SiO_2 thin films with cluster growth related to a specific defect feature. On a well-prepared SiO_2 thin film, gold nanoclusters preferentially decorate line defects. However, higher densities of Au nanoclusters are observed on the terrace sites of a SiO_2 thin film prepared at a lower annealing temperature. A plot of the number density of gold clusters with respect to Au coverage shows that the nucleation and growth of Au clusters is initially dominated by oxygen vacancy complexes [346].

Seed-mediated growth method [24] has been demonstrated to be a powerful synthetic route to generate a range of different types of metal nanoparticles [347]. This method separates the nucleation and growth stage of nanoparticle syntheses by introducing presynthesized small seed particles into a growth solution typically containing a metal precursor, reducing agent, surfactants, and some additives. It has been shown that various shapes of gold and silver nanoparticles (e.g., rods, spheres, cubes, and octahedra) can be synthesized using the method, depending on the type of surfactants and ionic additives (e.g., silver ions, halides, and hydroxide) in the growth solution [347]. This approach with hydroquinone can reduce HAuCl_4 in an aqueous solution that contains 15-nm gold nanoparticle seeds. This seed-based method of synthesis is similar to that used in photographic film development, in which silver grains within the film grow through addition of reduced silver onto their surface. Likewise, gold nanoparticles can act in conjunction with hydroquinone to catalyze reduction of ionic gold onto their surface. The presence of a stabilizer such as citrate results in controlled deposition of gold atoms onto the particles and growth. Typically, the nanoparticle seeds are produced using the citrate method. The hydroquinone method extends the range of monodispersed spherical particle sizes that can be produced. Furthermore, the hydroquinone method can produce particles of at least 30–300 nm.

Dissolution is one of the main processes that controls metal nanoparticles behavior in aquatic systems. This is not the case for the metal microparticles or bulk metal fragments. Dissolution of silver nanoparticles, for example, occurs through oxidation of metallic silver and release of Ag^+ into solution (or dissolution rate is accelerated) [348]. Release of Ag^+ is determined by intrinsic physicochemical properties of silver nanoparticles and by those of the solution. Parameters that either enhance or suppress silver nanoparticle dissolution are ionic strength, pH, dissolved oxygen concentration, temperature, dissolved complexing ligands (organic matter, sulfur, chlorine), silver surface coating, shape, and size [349]. Often dissolution of

silver (AgNPs) is controlled by a combination of solution and intrinsic properties making it challenging to evaluate contribution of each parameter to dissolution. Studies of silver nanoparticle dissolution in natural and synthetic waters revealed that particle size might have a dominant effect on AgNP dissolution. For instance, studies of AgNP dissolution in acetate buffer (pH 4) revealed more Ag^+ release from 4.8 nm than from 60 nm particles. Nevertheless, surface-area-normalized Ag^+ release was similar for both sizes suggesting that AgNP dissolution is size-controlled [350]. In general, the particle size has an inverse effect on AgNP dissolution: small nanoparticles (<15 nm) release more Ag^+ than large ones because particles of the smaller radius are energetically unfavorable due to higher surface-to-volume ratio and consequently more soluble [351].

Studies of PEG-SH-coated silver nanoparticle dissolution revealed that solubility of nanoparticles was larger in acetic acid than in water. The proposed mechanisms of silver nanoparticle dissolution are oxidative dissolution through reaction of metallic silver with dissolved oxygen and protons [348] following reactions:



Dissolution is initiated by oxidation of metallic Ag on the surface of AgNP by dissolved O_2 and formation of a 1–2 atomic layer thick silver(I) oxide (Ag_2O) [352]. The layer of Ag_2O dissolves releasing Ag^+ into solution until Ag_2O is extinguished [349]. Once the Ag_2O layer is completely dissolved, further oxidation of metallic Ag to Ag_2O might occur, and AgNP dissolution will continue. Our observation of increase of AgNP dissolution when pH decreased from 7 (water) to 3 (acetic acid) might further support formation of Ag_2O surface layer. In the presence of water, the surface of Ag_2O is covered with surface hydroxyl groups ($\text{Ag}-\text{OH}$) which undergo protonation at acidic pH ($\text{Ag}-\text{OH}_2^{2+}$). Protonation tends to weaken and break surface Ag–O bonds, resulting in larger Ag^+ release into solution at acidic than at neutral pH.

According to thermodynamic calculations, silver nanoparticles are not stable in aerobic waters with pH ranging from 4 to 12 and will dissolve completely [348]. The extent of dissolution varied between 3 and 15% in water and between 6 and 41% in acetic acid. Similar silver nanoparticle behavior was observed in other dissolution studies that found an extent of AgNP dissolution of 30% in acetate buffer (pH 4) [348], 10–27% in Hoagland medium (pH 5.6) [353], 11–52% in water (pH not reported) [352], and 1–60% in 1 M NaHCO_3 solution (pH 8) [354]. The results indicate that kinetic factors play an important role in inhibiting complete AgNP dissolution. Incomplete dissolution could be due to Ag^+ adsorption on AgNP, limited diffusivity of O_2 and protons to reaction sites, AgNP stabilization by PEG-SH, and particle aggregation. It was hypothesized that the partial dissolution of AgNP observed is due to an increase in the particle size leading to a solubility decrease. Analysis of AgNP by TEM revealed that the average diameter increased after dissolution of AgNP6, AgNP9, and AgNP13 and remained unchanged in

nondissolving AgNP70 (70 nm). The absence of size increase in the nondissolving AgNP70 suggested that release of Ag^+ during AgNP dissolution was necessary for the nanoparticle growth. Two possible mechanisms of AgNP size growth were considered: (1) precipitation of dissolved Ag^+ on the surface of AgNP and (2) Ostwald ripening. The first hypothesis was evaluated based on the XRD analysis of the 80 d-dissolved AgNP6, calculations of mass increase due to Ag^+ precipitation and saturation index calculations. The AgNP6 size increased from ~ 6.2 to ~ 10.6 nm by the end of dissolution experiment. Increase in dissolved Ag^+ concentration might shift Eq (2.18) equilibrium toward Ag_2O precipitation.

Experimental evidence of increase in average particle size as well as broadening of size distribution might indicate that Ostwald ripening was responsible for silver nanoparticle size growth [355]. Ostwald ripening is explained by the fact that larger particles with small surface-to-volume ratios are more stable than smaller particles with large surface-to-volume ratios, leading to dissolution of smallest particles and redeposition of the released atoms at larger particles. Growth of AgNP follows oxidation–reduction mechanisms, first smaller AgNPs are oxidized by O_2 , Ag^+ is then dissolved, followed by Ag^+ reduction and Ag deposition on larger AgNP [356]. Such mechanism would likely lead to a decrease in concentration of dissolved Ag^+ with time as observed in AgNP6 and AgNP9 samples. However, the dissolved Ag^+ concentration decrease, 5 and $0.8 \mu\text{M}$, would result in an average size growth to 7.2 and 9.5 nm in AgNP6 and AgNP9, respectively, which is smaller than the observed diameters at the end of dissolution experiment. The discrepancies in concentration changes and size growth suggest that oxidation of metallic silver and reduction of Ag^+ occurred simultaneously after reaching equilibrium. Similar observations were reported by Jang et al. [357] for Ostwald ripening of gold nanoparticles during which dissolved gold concentration did not change while particles increased in size. However, they were not able to determine what reducing agent was responsible for Ag(I) to Ag(0) transformation in the dissolution studies.

Jang et al. [357] studied Ostwald ripening of gold nanoparticles in the presence of H_2O_2 and Br^- . It was demonstrated that H_2O_2 induced both oxidation of smaller AuNP to Au(III) and Au(III) reduction leading to the increase in size of larger ones. Hydrogen peroxide production was detected during dissolution of citrate-coated AgNP in air-saturated water [348]. It was revealed that after a 3-h dissolution experiment, up to $0.4 \mu\text{M}$ H_2O_2 was produced in the presence of AgNP, while no H_2O_2 was detected in a control AgClO_4 solution. In the study of AgNP behavior in the presence of H_2O_2 , He et al. [358] observed reduction of Ag^+ at $\text{pH} > 5.5$. They demonstrated that the final AgNP increased in size, and the morphology changed from spherical to more irregular shape [358]. Thus, oxidative dissolution of AgNP might catalyze production of H_2O_2 , which further reduced Ag^+ to Ag atoms. Deposition of silver atoms on the AgNP surface resulted in the particle growth.

2.3 Biohybrids

QAC are the most extensively studied surface-active agents. They are mainly used as slimicides in swimming pools, antistatic agents in hair conditioners and wetting agents in nasal sprays. Moreover, they also find use shampoos and dishwashing materials [359]. The used surfactants find their way to various environmental segments and thus pose serious health hazards. They have the ability to adsorb strongly onto negatively charged suspended particulates and sludge. Intensive investigations have been carried out on their behavior, fate, and biological effects [143]. Long exposure to QACs can cause sensitization, hemolysis, and toxic effects by all routes of exposure including inhalation, ingestion, dermal application, and irrigation of body cavities. The concentrated solutions of QACs result in allergic reactions, hypersalivation, vomiting, hematemesis, and diarrhea. In severe cases, they may cause respiratory paralysis, convulsions, coma, and cardiorespiratory arrest [360].

Didodecyldimethylammonium bromide (DDAB) is toxic as well as cancer-preventing agent [361]. Toxicity is a major nuisance of anticancer drugs. Most of the clinically used anticancer drugs have a narrow therapeutic index, with a small difference in their dose for antitumor effect and toxicity. Therefore, the doses recommended for such compounds are determined according to their toxicity endpoints. Considerable research work has been carried out on the cancer prevention ability of DAAB but the mechanism of action has not been explored. The main cause of several diseases such as diabetes, hemophilia, and cancer is related to the alteration in the replication machinery of DNA. Therefore, drug interactions, with DNA which can affect the replication processes, are potential treatments for such ailments [362].

Polymer-based drug delivery systems emerged from the laboratory bench in the 1990s as a promising therapeutic strategy for the treatment of cancer and other devastating diseases [144]. Polymer–drug conjugates are nanosized hybrid constructs that covalently combine a bioactive agent with a polymer to ensure not only its efficient delivery to the required intracellular compartment but also its availability within a specific period of time. It has already been demonstrated that polymer–drug conjugation promotes tumor targeting by the enhanced permeability and retention effect and its capability of escaping from reticuloendothelial system. One promising example of such polymer nanomaterials is presented by a class of pluronic block copolymers (also known under nonproprietary name poloxamers). These block copolymers consist of hydrophilic poly(ethylene oxide) (PEO) and

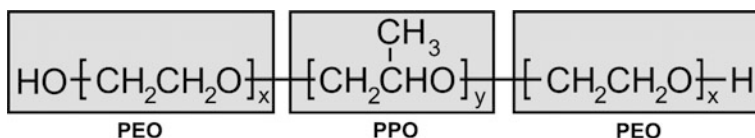


Chart 2.2 ABA tri-block structure of pluronic block copolymers

hydrophobic poly(propylene oxide) (PPO) blocks arranged in ABA tri-block structure: PEO-PPO-PEO (Chart 2.2) [363].

As outlined in a large number of previous reports, passive drug targeting is a validated method for improving the delivery of low molecular weight (chemo-) therapeutic agents to tumors [364]. Several different polymer-based anticancer agents have been approved for clinical use, including, e.g., Gliadel (i.e., carmustine-containing polymeric wafers, for surgical implantation in case of brain cancer), Lupron Depot (i.e., LHRH-containing polymeric microspheres, for local prostate cancer therapy), and Oncaspar (i.e., PEG-L-asparaginase, for the treatment of leukemia) [365]. For passive tumor targeting, however, essentially only Abraxane, i.e., albumin-based paclitaxel, has managed to be used (for metastatic breast cancer) [366]. This is in spite of the large number of passively tumor-targeted polymeric drug carriers that have been evaluated in animal models and in patients in the past two decades.

Prominent examples of macromolecular drug carrier systems evaluated in patients are albumin, poly(ethylene glycol), dextran, poly(L-glutamic acid), poly[N-(2-hydroxypropyl)methacrylamide], and others [367]. The most advanced of these formulations currently are, i.e., poly(L-glutamic acid)-based paclitaxel, which are in phase III trials for breast, ovarian, and lung cancers [368]. Copolymers based on N-(2-hydroxypropyl) methacrylamide (HPMA) were used to improve the tumor-directed delivery of doxorubicin and they demonstrated that long-circulating and passively tumor-targeted polymeric drug carriers are able to beneficially affect the therapeutic index of doxorubicin-based chemotherapy. These formulations were found to be 4–5 times higher than that of free doxorubicin, no cardiotoxicity was detected (in spite of the relatively high overall doses administered), and several clear responses were observed, in patients with nonsmall cell lung cancer, with colon cancer and with doxorubicin-resistant breast cancer [369].

At the preclinical level, a large number of additional HPMA-based nanodiagnostics and nanotherapeutics have been evaluated over the years, functionalized besides with standard chemotherapeutics, such as doxorubicin, cisplatin, and paclitaxel, also with more recently developed (and more sophisticatedly acting) drugs, such as the heat-shock protein inhibitor geldanamycin [370]. Moreover, besides passively tumor-targeted polymeric nanomedicines, also a large number of actively targeted HPMA copolymers have been designed and evaluated [371]. And furthermore, significant progress has also been made with respect to the development of novel drug linkers, such as pH-sensitive hydrazone spacers, which are much more effective than GFLG spacers in releasing doxorubicin, and which consequently much more strongly inhibit tumor growth [372].

HPMA copolymers have also been used for overcoming multidrug resistance [373], for coating viral and nonviral gene delivery systems [374], for imaging purposes [375], and for making block copolymer micelles, which can be core-cross-linked to improve their circulation times [376]. Furthermore, HPMA copolymers have also been employed to improve the treatment of noncancerous disorders, such as rheumatoid arthritis and bacterial infections, which are also characterized by a strong inflammation component and leaky blood vessels, and

which are therefore also highly amenable to EPR-mediated passive drug targeting [377]. And a significant number of studies have focused on the combination of HPMA copolymer-based nanomedicine formulations with other treatment modalities, such as with surgery, with radiotherapy, with hyperthermia, with photodynamic therapy, and with chemotherapy [378]. Together, these insights and efforts, HPMA copolymers are highly suitable systems for drug targeting to tumors. In addition, they indicate that by improving the pharmacokinetic and biodistributional properties of attached diagnostic and therapeutic active agents, long-circulating and passively tumor-targeted polymeric drug carriers might be suitable systems for image-guided drug delivery, as well as for improving the efficacy of combined modality anticancer therapy.

2.4 Conclusion

The field of NMNPs has been an extremely exciting research area for chemists, biologists, physicists, and materials scientists. This chapter attempted to give an outline of the colloid-chemical synthesis approach for controlling morphology in NMNPs. These nanoparticles with intriguing and novel morphologies, and sometimes with near-perfect shape control, have been produced by colloid-chemical synthesis. The influences of various synthesis parameters, processes, and approaches in manipulating the nanometer features in all three dimensions of nanoparticles have been discussed. Several viewpoints on how the particle morphology can be understood in terms of the precursor types and particle nucleation and growth have been compared and contrasted. This information will help to look at different aspects of particle morphology control in a more systematical way. We have touched upon some of the experimental tools and reaction mechanisms that provide the needed characterization of complex NMNPs.

Factors such as the nature and concentration of metal precursor and reducing agent, molar ratio of precursor to additives, the selective adsorption of additives to different crystal facets, contact with an external support, are all capable of influencing the nucleation and kinetics of particle growth. The proper choice of parameters for the reaction, including the temperature, radiation, the reducing method, the stabilizers (capping agent, surfactant, surface-active additive) and additives, plays a crucial role in the successful synthesis of metal nanoclusters. The metal ions from dissolved can be reduced, either by a chemical reductant (e.g., sodium borohydride, sodium hypophosphite), by light (photoreduction with visible or ultraviolet light), or by γ -rays (by radiolysis of water). Thus, the preparation of NMNPs by chemical reduction contains two major parts: (i) reduction using agents such as borohydrides, aminoboranes, hydrazine, formaldehyde, hydroxylamine, saturated and unsaturated alcohols, citric and oxalic acids, polyols, sugars, hydrogen peroxide, sulfites, carbon monoxide, hydrogen, acetylene, and monoelectronic reducing agents including electron-rich transition-metal sandwich complexes; and (ii) stabilization by agents such as trisodium citrate dihydrate, sulfur ligands (in

particular thiolates), phosphorus ligands, nitrogen-based ligands (including heterocycles), oxygen-based ligands, dendrimers, polymers, copolymers, and surfactants. Spectroscopic and microscopic techniques support a three-stage mechanism of NMNP formation. In the initial stage, simultaneous reduction and active nuclei formation are involved. This is followed by concurrent reduction, nucleation, and growth, and finally, single-crystalline nanoparticles are formed via growth by slow Ostwald ripening. The amount of stabilizing ligand influences the final nanoparticle size but has less effect on the nucleation and growth processes. The overall nanoparticle formation process becomes faster as the solution temperature increases, and the Ostwald-ripening growth mechanism is maintained.

It was reported that using citric acid as a reducing agent made the reduction reaction take one week longer and led to a wide size distribution. As far as stabilizers are concerned, citrate ions can bind on silver surfaces for shape control, but their ability to stabilize silver particles is weaker than thiols. Nowadays, a molecule which can act both as a reducing and capping agent is preferred so that the reaction takes place in one step and there is no need for an external reducing agent. This will reduce the number of steps involved in metal nanoparticle synthesis. The physical method involves radiation reduction of silver ions by γ -ray, microwave, ultraviolet, or visible light. Chemical reduction in solution is advantageous over other processes, because of its simplicity, low reaction temperature, and solubility of metal salts in water. Silver nanoparticles can be prepared in DMF without adding any reductant. It has been suggested that the reduction rate can be enhanced at high temperatures. Formamide is one of the most common solvents used to study various processes such as formation of metal nanoparticles, interaction with alcohols. The reducing power of the amines of several different structures was confirmed and showed, very clearly, that the oxidation potential of the reducing agent should lie between the oxidation of Au(0)–Au(I) and the reduction of Au(III)–Au(0) for the reaction to proceed. Multifunctional amines and nitrogen-containing polymers have also been tested for the synthesis of AuNPs. Ketyl radicals formed by the photolysis of carbonyl-based initiator acted as reductants of silver salt leading to the formation of AgNPs. This approach is based on the Norrish Type I photocleavage of photoinitiator leading to ketyl radicals. Silver cations, Ag^+ , scavenge the $(\text{CH}_3)_2\text{C}^\bullet\text{OH}$ radical (ketyl) and reduce Ag^+ to Ag^0 . It was postulated that this protecting effect depends on the number of available NH_2 groups, rather than the macromolecule conformation.

Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymers are well known as dispersion stabilizers and templates for the synthesis of mesoporous materials and nanoparticles. Variation of the PEO-PPO-PEO block copolymer molecular characteristics, concentration, and temperature allows for unique tunability of block copolymer self-assembly in the presence of selective solvents such as water. It was found that PEO-PPO-PEO block copolymers can act as very efficient reductants/stabilizers in the single-step synthesis and stabilization of gold nanoparticles from gold salts. Formation of gold nanoparticles from AuCl_4^- in aqueous PEO-PPO-PEO block copolymer solutions includes three main steps: (1) reduction of metal ions in aqueous block copolymer

solution (2) absorption of block copolymer on gold clusters because of amphiphilic character (hydrophobicity of PPO) and reduction of further metal ions on the surface of gold clusters, and (3) growth of gold particles and stabilization by block copolymers. Furthermore, copolymers (as capping agents) with stimulus responsibility have attracted growing attention due to their diverse self-assembly behavior in response to stimuli, such as pH, temperature, salt. The stimulus responsibility allows for tailoring the supramolecular aggregates with desirable morphologies and properties from the same precursory copolymers. Poly(*N*-isopropylacrylamide) is a stimulus responsive polymer that undergoes a reversible, inverse phase transition at a lower critical solution temperature in pure water. In addition to temperature, cosolvents can also cause an inverse phase transition in pNIPAM. The functionality of pNIPAM on surfaces can be separated into two categories: (1) triggered changes in polymer conformation and (2) triggered changes in polymer surface energetics.

Coordination chemistry offers simplicity, stable bonding, and ligand-metal specificity, enabling ligand-bearing components to be assembled into supramolecular structures using appropriate metal ions. This approach is particularly compatible with surface chemistry, as binding of metal ions activates the surface toward ligand binding, and vice versa. The reactive ligands approach highlights that (i) the ligands decorated on a spatially limited surface can be used for further chemistry, and the rest of the ligands can be selected to remain unreactive during the coupling process. (ii) It was applicable to a wide size range of nanoparticles, e.g., the functionalization of AuNPs with the diameter of 16–41 nm was demonstrated.

In addition to the stabilizing ability of some stabilizing agents, BSA and HSA, these additives can also be used as a reducing agent. A protein macromolecule contains several amino acids such as cysteine, tryptophan, lysine which can act as weak reducing agents. All these amino acids can reduce gold or silver ions independently even at room temperature. However, when amino acid is present in a protein macromolecule, the reducing ability is significantly compromised by the steric screening of other nonreducing amino acids in the vicinity. Then, the reducing ability of a particular amino acid is purely related to its location in the native state of protein.

In the pullulan- and chitosan-mediated synthesis procedure, these modified nanoparticles were first produced and gold layers were then added to promote the anisotropic growth, which is indeed, substantially sensitive to the presence of the chitosan matrix. Their reducing and stabilizing activities led to the one-pot procedure. The appropriate amounts of iron particles and chitosan solution enabled the fine control of the chitosan-mediated approach leading to a high product yield of anisotropic nanoparticles. The proposed synthesis procedure remains simple, and the reaction carried out at room temperature allows to obtain core-shell nanoparticles of around ~ 90 nm diameters with narrow size distribution. Chitosan acts as a soft template in the formation of multibranched magnetic nanoparticles, and gold coating process was carried out in the presence of chitosan to give better particle dispersity and to avoid agglomeration problems.

A novel approach has been developed for the preparation of diverse libraries of ligand-stabilized metal nanoparticles that address the challenges stated above. It

consists of a straightforward two-step procedure, involving (i) preparation of well-defined phosphine-stabilized precursor particles (d_{CORE}) and (ii) functionalization of these particles through ligand exchange reactions with functionalized thiols.

In a typical liquid-phase synthesis, the nanoparticle formation process undergoes three distinct stages as follows: (1) reduction and generation of active nuclei, (2) formation of seed particles upon collision of active nuclei, and (3) formation of larger nanoparticles via a growth process, which may be Ostwald ripening or aggregation. The NMNP growth is generally categorized by two processes: diffusion-controlled Ostwald ripening and aggregation/coalescence. The diffusion-controlled Ostwald-ripening growth can be differentiated from the aggregative/coalescence growth by three distinct observable characteristics during the nanoparticle formation as follows: (1) The final nanoparticles should be single crystalline in nature, (2) the nanoparticle growth kinetics should be nonsigmoidal, and (3) the early reduction process should not involve a bimodal size distribution.

Dissolution of silver nanoparticles, for example, occurs through oxidation of metallic Ag and release of Ag^+ into solution (or dissolution rate is accelerated). Release of Ag^+ is determined by intrinsic physicochemical properties of AgNP and by those of the solution. Parameters that either enhance or suppress AgNP dissolution are ionic strength, pH, dissolved oxygen concentration, temperature, dissolved complexing ligands (organic matter, sulfur, chlorine), silver surface coating, shape, and size. The proposed mechanisms of AgNP dissolution are oxidative dissolution through reaction of metallic Ag with dissolved oxygen and protons. Protonation tends to weaken and break surface Ag–O bonds, resulting in larger Ag^+ release into solution at acidic than at neutral pH. Two possible mechanisms of AgNP size growth were considered: (1) precipitation of dissolved Ag^+ on the surface of AgNP and (2) Ostwald ripening. Growth of AgNP follows oxidation–reduction mechanisms, first smaller AgNPs are oxidized by O_2 , Ag^+ is then dissolved, followed by Ag^+ reduction and Ag deposition on larger AgNP.

It was found that the temperature plays a decisive role in the synthesis of bimetallic Au–Pt nanoparticles protected with PVPo by the polyol method. It does not only affect the rates of reduction and nucleation of the metals, but it also affects the coordination between the metals and the polymeric protective agent, the distribution of elements in the nanoparticles, and the final particle size.

We have demonstrated the synthesis of silver nanoparticles in formamide at room temperature without adding any reductant from outside. In the presence of a proper stabilizer, nanoparticles of silver metal can be stabilized. Surface-modified particles (or films) show optical properties significantly different from those of the primary silver dispersion (or film). The silver nanoparticles also act as redox catalysts due to the shift in the Fermi level toward more negative potential. Moreover, the method described here presents a simple approach for the formation of silver nanoparticles.

To obtain MNP composites through the efficient, convenient, and easy way, a one-step approach based on the interfacial thiol–ene photopolymerization, in which microcapsules (MCs) and metal nanoparticles are generated simultaneously by irradiation of ultraviolet (UV) light, was developed. The in situ photoreduction of metal ions can minimize the number of processing steps in fabrication of metal nanoparticles. A series of gold, silver, and platinum nanoparticle-decorated microcapsules (MC@AuNPs, MC@AgNPs, and MC@PtNPs) were prepared through this one-step interfacial thiol–ene photopolymerization. AgNO₃ can be intercalated into the gallery regions of montmorillonite and formed hybrid framework. These MMT@AgNPs nanocomposites exhibited card-like and ball-like homogeneous surface fractions and form one-phase morphology. The degree AgNPs dispersion on MMT surface is a function of color intensity and its homogeneity. The stable AgNP@MMT nanocomposites were synthesized by microwave method. XRD analyses and TEM observations confirmed the formation of nanoparticles on the clay surfaces.

Ionic liquids (ILs) are a viable option as stabilizing agents because of their ionic character and can be easily made task-specific as phase-transfer catalysts due to their tunable nature. They are used to halt aggregation of Au(0) produced in the reduction of tetrachloroauric acid, thus limiting the size of the gold aggregates that form nanoparticles. Room-temperature ionic liquids are attracting much interest in many fields of chemistry and industry, due to their potential as a “green” recyclable alternative to the traditional organic solvents. They are nonvolatile and provide an ultimately polar environment for chemical synthesis. Among various known ionic liquids, ionic liquids containing imidazolium cation and PF₆[−] have a particularly useful set of properties, being virtually insoluble in water. We have demonstrated the synthesis of the imidazolium ionic liquid-modified gold nanoparticles.

Well-defined, single, dispersed, structurally unusual, tadpole-shaped gold nanoparticles were synthesized by the reduction of chloroauric acid with tri-sodium citrate in the presence of a capping agent such as sodium dodecylsulfonate. TEM and AFM images show a clear view of its three-dimensional (3D) stereographic structure. It can be easily inferred from these images that the head and tail of the nanotadpole possess different structures (poly- and single-crystalline, respectively), but the tadpole-shaped object as a whole maintains polycrystalline.

The initial monomodal size distribution of gold nanoparticles changed into a bimodal one during pulsed laser irradiation. This modal change was caused by the gradual size reduction of gold nanoparticles. From careful observation by TEM, we extracted a characteristic value for the size-reduction rate per one pulse. It was revealed that the size reduction of gold nanoparticles under picosecond laser pulses occurred even below the boiling point because of the gold vapor formation around hot liquid gold drops. With sufficient laser energy for the boiling of particles, gold vapor can also be formed inside liquid gold drops, and such bubbles go to the outside of the drops with some volume of liquid gold around the bubbles, resulting in the formation of particles with gold strings on their surfaces. Obtained results

also indicate that the important factor that determines the phenomenon is not temperature but the vapor pressure at the liquid interface. The condensation process of gold vapor is thought to be one of the main factors that restricts the sizes of small particles.

The field of NMNPs has been an extremely exciting research area for chemists, biologists, physicists, and materials scientists. This chapter attempted to give an outline of the colloid-chemical synthesis approach for controlling morphology in NMNPs. NMNPs with intriguing and novel morphologies, and sometimes with near-perfect shape control, have been produced by colloid-chemical synthesis. The influences of various synthesis parameters in manipulating the nanometer features in all three dimensions of NMNPs have been discussed. Several viewpoints on how the particle morphology can be understood in terms of the seed structure, surface energies of various crystallographic planes, relative growth rates along various crystallographic directions, and so forth, have been compared and contrasted. This information will help to look at different aspects of particle morphology control in a more systematical way. Reliable characterization of nanoparticles is one of the most important aspects of nanoparticle synthesis. We have touched upon some of the experimental tools that provide the needed characterization of complex NMNPs.

The progress in the NMNP synthesis has been rapid and inspired toward the innovative synthesis methods and sophisticated characterization techniques. However, most of the methods are limited to synthesis in small quantities and often have poor yield of a given morphology. Colloid-chemical synthesis very often results in a mixture of nanoparticles and constant efforts must be directed to gain exquisite control of the size and the shape of various types of nanoparticles. Achieving high yield and successful scaling up of the synthesis process are necessary for the synthesis to be commercially viable. At the same time, there is need for the development of advanced techniques for separation or elimination of the unwanted shapes.

The used precursors (mainly surfactants) find their way to various environmental segments and thus pose serious health hazards. They have the ability to adsorb strongly onto negatively charged suspended particulates and sludge. Intensive investigations have been carried out on their behavior, fate, and biological effects. They can be toxic and used as well as cancer-preventing agent. Toxicity is a major nuisance of anticancer drugs. Most of the clinically used anticancer drugs have a narrow therapeutic index, with a small difference in their dose for antitumor effect and toxicity. Prominent examples of macromolecular drug carrier systems evaluated in patients are albumin, poly(ethylene glycol), dextran, poly(L-glutamic acid), poly [*N*-(2-hydroxypropyl)methacrylamide], and others. Copolymers based on *N*-(2-hydroxypropyl)methacrylamide (i.e., HPMa) and PEO-PPO were used to improve the tumor-directed delivery of doxorubicin and they demonstrated that long-circulating and passively tumor-targeted polymeric drug carriers are able to beneficially affect the therapeutic index of doxorubicin-based chemotherapy.

Glossary

Chemotherapy	as a treatment of cancer often relies on the ability of cytotoxic agents to kill or damage cells which are reproducing. This cancer treatment uses one or more anticancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. Chemotherapy is one of the major categories of medical oncology (the medical discipline specifically devoted to pharmacotherapy for cancer).
Chemotherapeutic agents	are also known as cytotoxic agents. These are generally used to treat cancer. It includes alkylating agents, antimetabolites, antitumor antibiotics, anthracyclines, and topoisomerase inhibitors.
Chemotherapeutics	such as doxorubicin, cisplatin, and paclitaxel are selectively destructive to malignant cells and tissues.
Cross-link	is a bond that links one polymer chain to another. They can be covalent bonds or ionic bonds. When the term “cross-linking” is used in the synthetic polymer science field, it usually refers to the use of cross-links to promote a difference in the polymers’ physical properties. When “cross-linking” is used in the biological field, it refers to the use of a probe to link proteins together to check for protein–protein interactions, as well as other creative cross-linking methodologies.
DNA replication	is the biological process of producing two identical replicas of DNA from one original DNA molecule. This process occurs in all living organisms and is the basis for biological inheritance. DNA is made up of a double helix of two complementary strands. During replication, these strands are separated. Each strand of the original DNA molecule then serves as a template for the production of its counterpart. Cellular proof-reading and error-checking mechanisms ensure near perfect fidelity for DNA replication.
Hemolysis	or haemolysis, also known by several other names, is the rupturing (lysis) of red blood cells (erythrocytes) and the release of their contents (cytoplasm) into

	surrounding fluid (e.g., blood plasma). Hemolysis may occur in vivo or in vitro (inside or outside the body).
Metastatic cancer, or metastatic tumor,	is one which has spread from the primary site of origin (where it started) into different area(s) of the body. Metastasis is the spread of cancer cells to new areas of the body (often by way of the lymph system or bloodstream).
Photodynamic therapy (PDT)	is a clinically approved and minimally invasive therapy that uses a nontoxic light-sensitive compound (photosensitizer) that is readily absorbed by abnormal cells. When exposed to a specific wavelength of light, the photosensitizer is activated to produce changes in endothelial cell integrity that ultimately produces vascular disruption.
Rheumatoid arthritis (RA)	is a long-lasting autoimmune disorder that primarily affects joints. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Sulfasalazine is a chemical that prevents the growth of slime in paper stock.
Spacer	the most developed peptide linker for triggered release of covalently attached drug is the glycylphenylalanylleucylglycine (GFLG) tetra-peptide spacer. This spacer is often employed in published polymer anticancer conjugates based on <i>N</i> -(2-hydroxypropyl) methacrylamide (HPMA).
Therapeutic index (TI)	(also referred to as therapeutic ratio) is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity. The related terms therapeutic window and safety window refer to a range of doses which optimize between efficacy and toxicity, achieving the greatest therapeutic benefit without resulting in unacceptable side effects or toxicity.

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and Collective Properties

Capek, I.

2017, XVII, 554 p. 210 illus., 91 illus. in color.,

Hardcover

ISBN: 978-4-431-56554-3