Chapter 1
Synthesis of Metallic and Metal Oxide Particles

Kateryna Loza and Matthias Epple

Abstract The diversity of applications in catalysis, energy storage and medical diagnostics utilizes unique and fascinating properties of metal and metal oxide nanostructures. Confined to the nanometer scale, materials may display properties that are different from the equivalent bulk compounds. To meet the requirements for various applications, numerous production techniques were developed to control particle size, morphology, aggregation state, crystal structure, surface charge and composition. This chapter presents an overview of the preparation of metallic and metal oxide nanoparticles by bottom-up and top-down approaches. We describe basic synthetic routes for prominent cases of metals (gold, silver, platinum and copper) and metal oxides (zinc oxide, titania, and silica).

1.1 Introduction

Metal nanostructures attract particular interest because of their unique and fascinating properties compared to their bulk counterparts. The variety of applications comprises biological sensing [1, 2], imaging [3–9], medical diagnostics [10–12], cancer therapy [13, 14], catalysis [15, 16], and energy storage [17, 18]. The observed new chemical, optical, and thermal properties of metallic nanoparticles occur when the size is confined to the nanometer length scale [19]. Numerous techniques were developed to produce metal nanoparticles to meet the requirements for various applications. In general, there are two strategies to manufacture materials on the nanoscale: "Top-down" and "bottom-up" (Fig. 1.1) [20, 21]. The first method is based on breaking down a system (i.e., the bulk material) into smaller units. Common "top-down" techniques are lithography, milling, ultrasound treatment, and laser ablation. These processes

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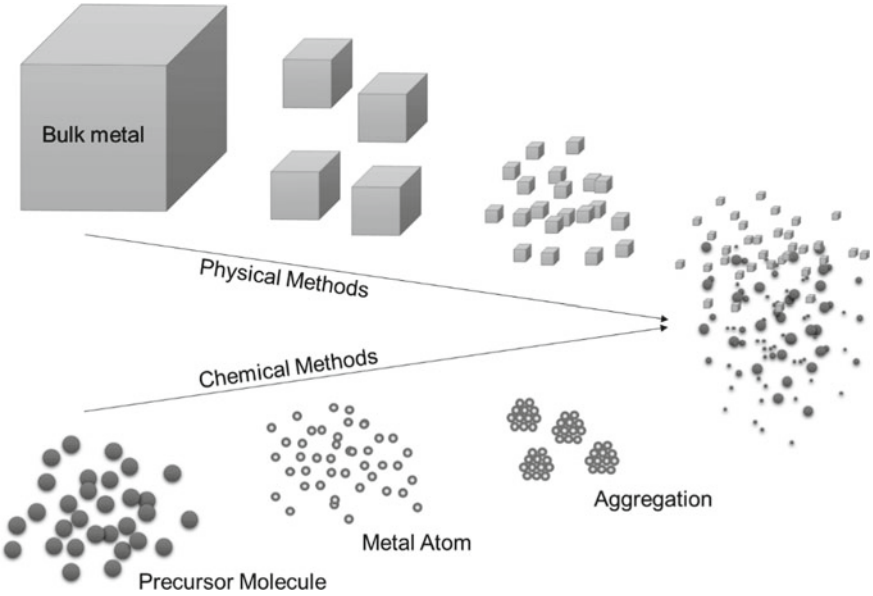

Fig. 1.1 Schematic illustration of synthetic methods for metal nanoparticles. (Adapted with permission from New J. Chem., 1998, 1179–1201. Copyright 1969 The Royal Society of Chemistry) [22]

are comparatively simple and usually lead to ligand-free ("naked") nanoparticles. However, there is a limited control over the manufacturing process, e.g., an exact size or shape adjustment of resulting particles. The "bottom-up" method relies on material synthesis from atomic or molecular species via a suitable chemical reaction, allowing the particles to grow from smaller units. This approach uses the chemical properties of single molecules or atoms to cause self-organization into the desired particle shape.

The "bottom-up" approach is commonly associated with wet-chemical methods, because colloidal metallic particles are commonly produced by chemical reduction of metal salts dissolved in a suitable solvent in the presence of surfactants or ligands that cover the surface [23]. A wide range of reducing agents have been used in the colloid-chemical synthesis of metal nanoparticles [24]. For example, H_2, hydrazine, hydroxylamine, hydrides (e.g. $NaBH_4$ or B_2H_6), ascorbic acid or ascorbate, citric acid or citrate, reducing polymers (e.g., PVA) and solvents (like alcohols, diols, aldehydes, and DMF) have been used to prepare metal nanoparticles [25–29]. Reduction can take place at room temperature or at elevated temperatures, depending on the relative reduction potentials of the precursor and the reducing agents [30–33].

In the following, we discuss the cases of gold, silver, copper, and platinum as representative examples, and also the preparation of alloyed nanoparticles by various synthetic methods. The described methods can typically be transposed to other kinds of nanoparticles, typically of noble metals.

1.2 Metals (Gold, Silver, Platinum and Copper)

1.2.1 Gold

The first systematic synthesis of Au colloids was reported 160 years ago by Michael Faraday using phosphorus to reduce $AuCl_4^-$ ions [34]. In the 1950s, an easier approach was established and standardized by Turkevich [35]. He used the mildly reducing agent trisodium citrate, added to a boiling aqueous solution of $HAuCl_4$, to obtain monodisperse gold nanoparticles in the size range from 10 to 40 nm. Due to its simplicity, this synthesic method was adapted in many variations [36, 37]. For example, switching to a mixture of reducing agents (e.g. citrate and tannine) allows to clearly shorten the reaction time and to enhance the stability of the formed colloid [38, 39].

The reduction of tetrachloroauric acid in an aqueous medium is a versatile synthetic route and possible with many different reducing agents like sodium borohydride ($NaBH_4$), ascorbic acid, and hydroquinone [40–42]. The use of $NaBH_4$ as reducing agent results in a fast reduction and a gold particle size of 1–5 nm [29, 43, 44]. In general, the choice of the reducing agent has a strong influence on the resulting particle size, since with increasing reduction potential the number of the formed nuclei increases and the growth of particles is limited. On the nanometer scale, metals tend to nucleate and grow into multiply twinned particles with their surfaces defined by the lowest-energy facets [45]. Anisotropic gold nanoparticles (rod-, rectangle-, hexagon-, cube-, triangle- and star-like shapes) with less stable facets were kinetically achieved by adding chemical capping reagents, i.e. agents that selectively block certain crystal faces, to the reaction mixture [25, 46, 47].

The previously described methods are based on a synthesis from atomic or molecular species by chemical reaction, so called “bottom-up” approach. In liquid media, dispersed metallic nanoparticles can be generated by the pulsed laser ablation process, a “top down” technique [48]. This method provides ligand-free nanoparticles [49]. The size of obtained particles can be varied to some extent by the laser parameters and by subsequent laser fragmentation steps [50, 51]. Furthermore, an in situ conjugation of nanoparticles with biomolecules by laser ablation in an aqueous medium is a highly promising one-step method for the production of functional nanoparticles [52].

The polydispersity of nanoparticles is a key concern in nanoscience research. Even though reasonably monodisperse nanoparticles can be produced, usually not all nanoparticles are fully identical (see Fig. 1.2 for an example). This fact leads to the ultimate aim for a synthesis of atomically precise nanoparticles [53]. In the case of gold, this was accomplished for ultrasmall gold nanoparticles (containing 10–300 atoms, often called nanoclusters) [54, 55]. Several groups established synthetic routes to produce a gold core in the size range of 1–3 nm. Such ultrasmall nanoparticles are typically formed by metal salt reduction in the presence of phosphanes (PR_3) [56, 57] or thiols (HS–R) [44]. Exerting a strict control over the size of a cluster strongly affects the activity and the selectivity in a catalytic process [58]. Furthermore, a

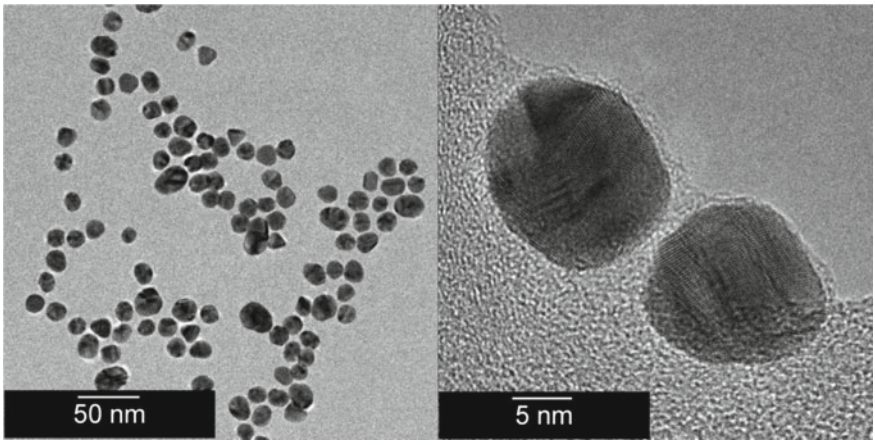

Fig. 1.2 Transmission electron micrographs of PVP-stabilized gold nanoparticles, prepared by the standard citrate method after Turkevich. (Reproduced from the dissertation of D. Mahl, 2011, University of Duisburg-Essen) [60]

supracolloidal self-assembly of atomically precise nanoparticles is a promising platform for novel 2D and 3D materials with additional plasmonic functionalities, novel mechanical properties, and inherent flexibility [59].

1.2.2 Silver

Colloidal silver is known since about 120 years [61]. The manufacturing of silver nanoparticles can be done by physical processes such as ultrasonication, chemical vapor deposition, or pulsed laser ablation in liquids [62–64]. However, wet-chemical "bottom-up" syntheses offer more possibilities for the variation of particle size, morphology and functionalization. The most commonly used precursor for preparing silver nanoparticles in wet-chemical reductions is silver nitrate ($AgNO_3$) because of its high solubility in many polar solvents and dispersability in less polar solvents, sometimes after adding surfactants and/or using ultrasonication. The reducing agents used in the synthesis of nanoparticles from silver(I) ions are comparable to those used for gold nanoparticle preparation. Already in 1889, M. C. Lea published the synthesis of citrate-stabilized silver nanoparticles [65]. In general, one-pot methods for the reduction of silver nitrate have evolved, where different reducing agents such as sodium citrate [66], glucose [67], ascorbate [68], sodium borohydride [69, 70], polyols [71, 72], and ammonium formiate were used [73]. Typically, the reactions are performed at elevated temperatures by conventional heating in an oil bath. Alternatively, microwave-assisted syntheses can increase the reaction rates and yields as well as selectivity and reproducibility [30].

The particle properties depend not only on their size but also on their morphology. As a result, a shape-controlled synthesis of silver nanoparticles is of special

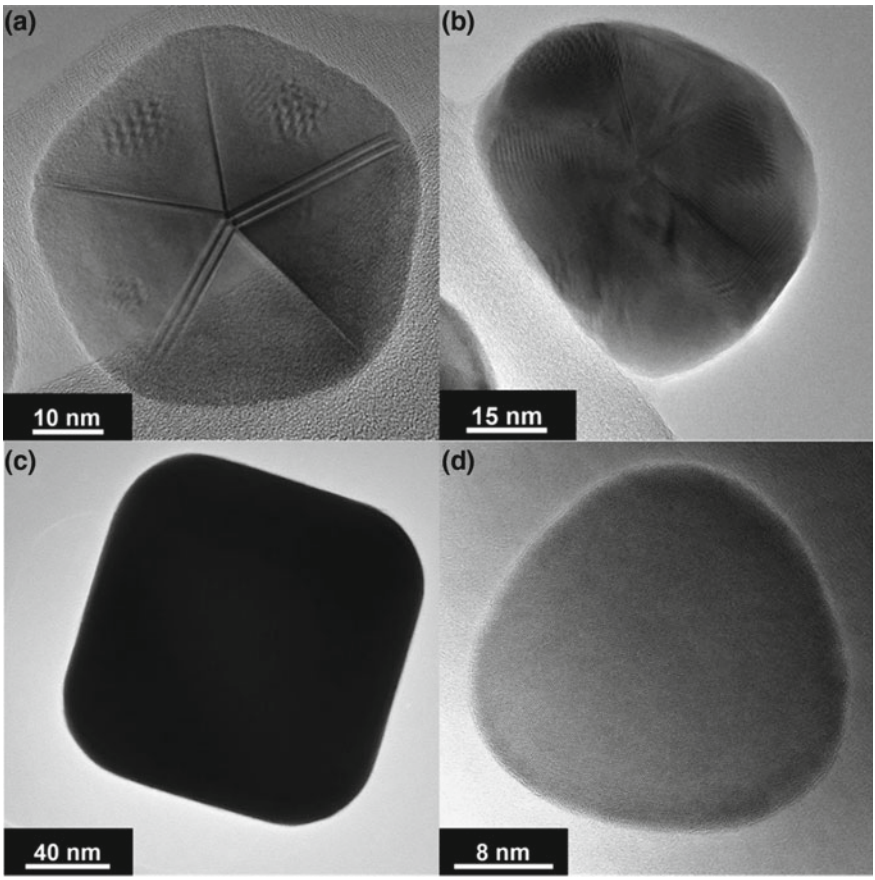

Fig. 1.3 Transmission electron micrographs of different kinds of PVP-stabilized silver nanoparticles, prepared by glucose reduction (**a**) [67], a microwave-assisted reduction (**b**) [30], a modified polyol synthesis (**c**) [79], and a microwave-assisted modified polyol process (**d**) [80]. (Adapted with permission from Cryst. Growth Des. 16, 7, 3677–3687. Copyright 2016 American Chemical Society) [81]

interest. Xia et al. and others described the structural evolution of silver nanoseeds to nanoparticles with defined shapes like platelets [74], cubes [75], rods [76], rings [77], and bipyramids [78] (Fig. 1.3).

It is critical to understand not only the growth mechanism of nanostructures, but the process of seed formation, because the number of twin planes in the initial stage is the key factor for determining the shape of the final product (single-crystal seeds form cubes, multiply-twinned decahedral seeds form wires) [82].

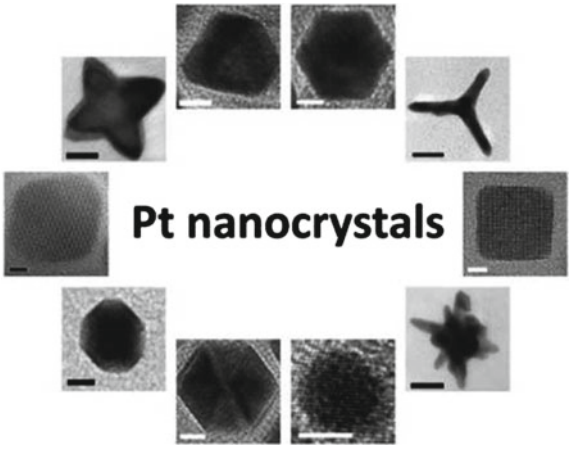

Fig. 1.4 Transmission electron micrographs of platinum nanoparticles, prepared by solution-phase synthesis using metal carbonyls as reducing agents. This synthetic method produces highly monodisperse Pt octahedral, icosahedra, cubes, truncated cubes, cuboctahedra, spheres, tetrapods, star-shaped octapods, multipods, and hyper-branched structures. (Reproduced with permission from ACS Nano 7, 1, 645–653. Copyright 2012 American Chemical Society) [89]

1.2.3 Platinum

Platinum nanostructures are of particular interest for many industrial applications due to their extraordinary catalytic properties in various industrial syntheses like petrochemistry or energy conversion [83–86]. Conventional techniques to prepare platinum nanoparticles are based on wet-chemical methods [87–89]. Typically, the reaction involves the reduction of a Pt(II) precursor (like K_2PtCl_4 or $Pt(acac)_2$) or a Pt(IV) precursor (like K_2PtCl_6) in the presence of a stabilizing polymer by reducing agents such as hydrogen [90], carbon monoxide [91], sodium borohydride [92], lithium borohydride [93], and ethylene glycol [94]. The resulting nanoparticles may be considered as monodisperse in size, but they are often irregular in shape and lack well-defined facets [95]. Further modifications may include sonication during the reaction [96] or microwave-assisted heating [94]. Because the reactivity and the selectivity of Pt nanoparticles are highly dependent on the exposed facets [97], the synthesis of uniformly shaped particles is decisive for high catalytic performance [98]. Their morphological evolution is often controlled by the reduction kinetics of the platinum precursor [95], the reaction temperature [98], or the use of shape-directing reagents [99, 100] (Fig. 1.4).

The previously syntheses were based on the “bottom-up” approach. However, chemical synthesis methods often lead to impurities of the nanoparticle colloids caused by additives and precursor reaction products [101]. In contrast, Barcikowski et al. demonstrated the preparation of ligand-free platinum nanoparticles by laser

ablation in liquids ("top-down" technique) for the surface modification of electrodes for neural stimulation [102].

1.2.4 Copper

Since the ninth century, copper nanoparticles are known as coloring agents in Mesopotamia [103]. Nowadays the application range comprises biomedicine [104, 105], sensors [106], conductive inks [107], and organic catalysis [108–110]. Being inexpensive and rather abundant in nature, copper is utilized in large scale for the fabrication of plasmonic solar cells [111]. Recently established methods for copper nanoparticle synthesis include laser ablation [112], thermal decomposition [113], the polyol process [114, 115], and other chemical reduction methods [116]. Typical precursors for copper nanoparticle wet-chemical syntheses are $CuSO_4$, copper acetylacetonate ($Cu(acac)_2$), $CuCl_2$, and $Cu(NO_3)_2$ [117]. Reducing agents comprise ascorbic acid [118], sodium borohydride [119], and hypophosphite [120]. It should be mentioned that the preparation of Cu nanoparticles is challenging due to its high sensitivity to air because copper is easily oxidized to copper oxides, being less noble than silver, gold, or platinum metals [121]. The oxidation of copper nanoparticles can be avoided if the synthesis is conducted in non-aqueous media (sometimes under inert gas) and in the presence of CO or H_2. Previously described synthetic routes result in spherical multi-twinned nanoparticles in the size range between 10 and 70 nm. As shown in Fig. 1.5, by variation of the ratio of copper acetylacetonate to oleylamine, different particle size distributions can be achieved. If a hydrothermal treatment is applied, anisotropic copper particles such as nanowires or nanorods can be produced [110].

1.3 Alloyed Nanoparticles

The properties of metallic systems can be significantly extended by mixing elements to generate intermetallic compounds and alloys. Due to synergetic effects, an enhancement in desired properties is possible. The diversity of compositions, structural organizations, and tunable properties of metallic alloys makes them suitable for a wide range of applications in electronics, engineering, biomedicine, and heterogeneous catalysis [123–126]. For example, alloyed silver and gold nanoparticles utilize the physicochemical properties of both metals, e.g., the optical properties of gold and the toxicity towards bacteria or cells of silver [127, 128]. Surface structure, composition, and segregation properties [129] of nanoalloys are of great importance for the chemical reactivity and the selectivity in catalysis [130, 131]. If confined to the nanometer scale, they may display properties that are different from the equivalent bulk compounds. For example, iron and silver are immiscible in the bulk, but can be mixed in nanoparticles [132] (Fig. 1.6).

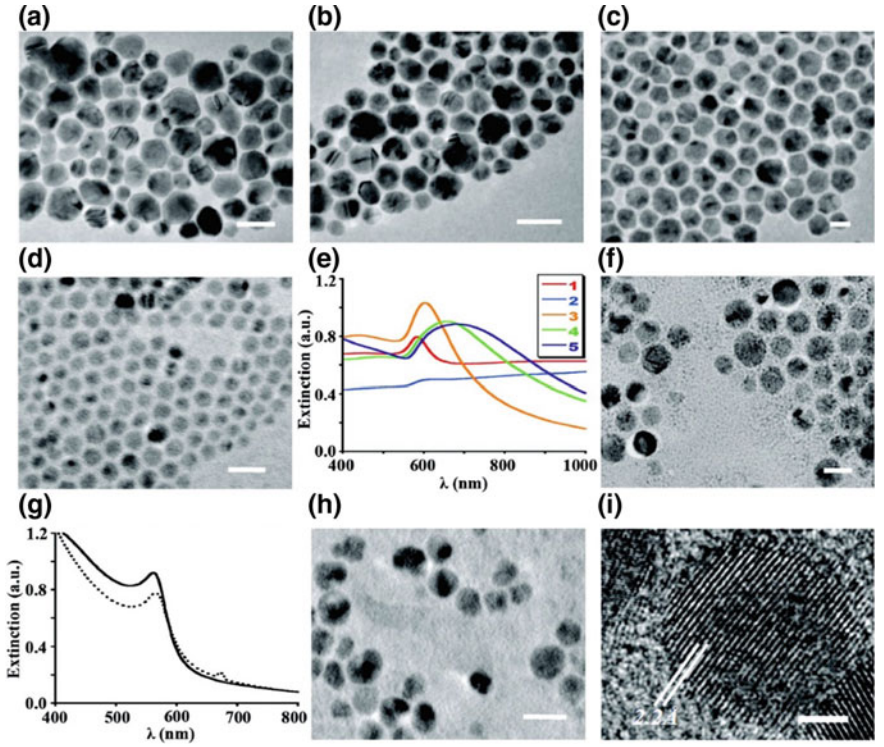

Fig. 1.5 Transmission electron micrographs and UV/VIS spectra of copper nanoparticles, prepared with different ratios of copper acetylacetonate and oleylamine. Scale bars in **a** and **b** are 50 nm, those in **c**, **d**, **f**, and **h** are 20 nm, and that in **i** is 2 nm. (Reproduced with permission from J. Phys. Chem. C, 2010, 114 (37), pp 15612–15616. Copyright 2010 American Chemical Society) [122]

Due to the heterogeneity of different properties of individual components (e.g., crystal system, redox potential, crystal symmetry, or surface charge), the successful mixture of these materials into a finite nanoparticle is challenging [123, 133]. In general, the methods for preparation of nanoalloys are the same as for single metal nanoparticles. Ligand-free manufacturing methods of nanoparticles are based on laser ablation of solids in liquid environment [134, 135], pulsed arc discharge, and sputtering techniques [123]. These approaches start with single, bimetallic or ternary targets or mixed metallic powders. Figure 1.7 shows a typical setup and the obtained alloyed Ag/Au nanoparticles by laser ablation in liquids.

Bimetallic colloids can be generated by chemical reduction of a suitable mixture of salts (metal precursor) in the solution, using appropriate reducing agent. To avoid the formation of core-shell structures due to the difference in redox potentials, different ligands can be used [137]. Another variation is based on the reduction of double metal complexes [22]. Instead of chemical reduction, an electrochemical process can be

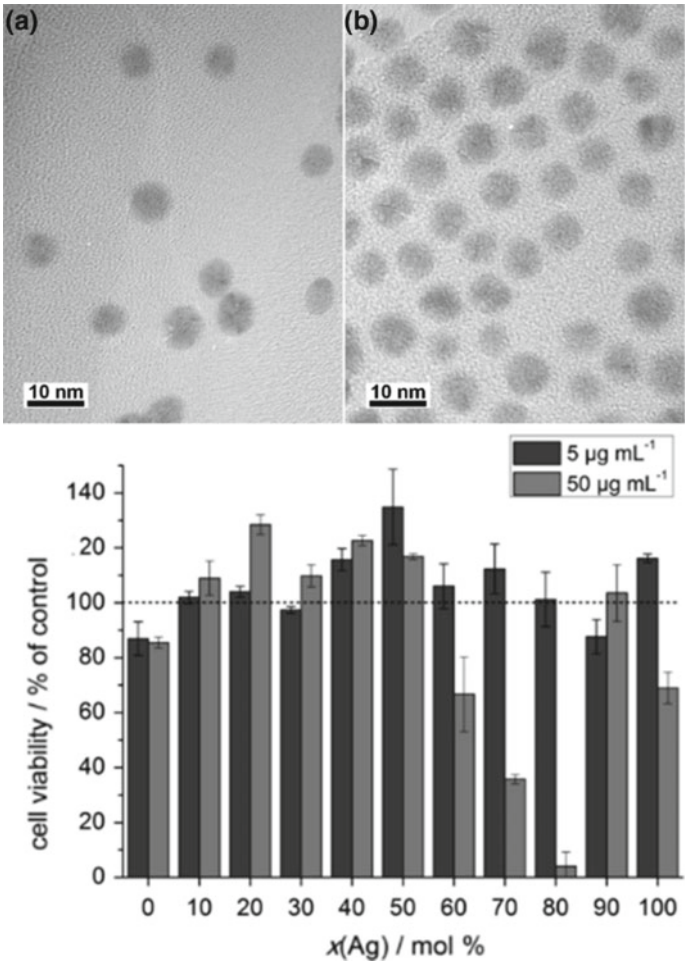

Fig. 1.6 Transmission electron micrographs of PVP-functionalized Ag/Au alloyed nanoparticles and the viability of HeLa cells after incubation with alloyed nanoparticles. Note that the cytotoxicity is not proportional to the relative silver amount, pointing to special effects that occur in the alloyed nanoparticle beyond a mere additivity of the metal properties. (Adapted from Beilstein J. Nanotechnol. 2015, 6, 1212–1220; © 2015 Ristig et al.; licensee Beilstein-Institut) [127]

used to create metal atoms from bulk metal. The particle size was be controlled by the current density [138].

Seeded-growth techniques permit the synthesis of core-shell nanoparticles [139]. As seen from Fig. 1.8, Pd–Au core-shell nanoparticles can be prepared by a water-based one-pot synthesis, followed by a stabilization with poly(N-vinyl pyrrolidone). Here, a sequential metal deposition with a distinct boundary between both metals was achieved [140].

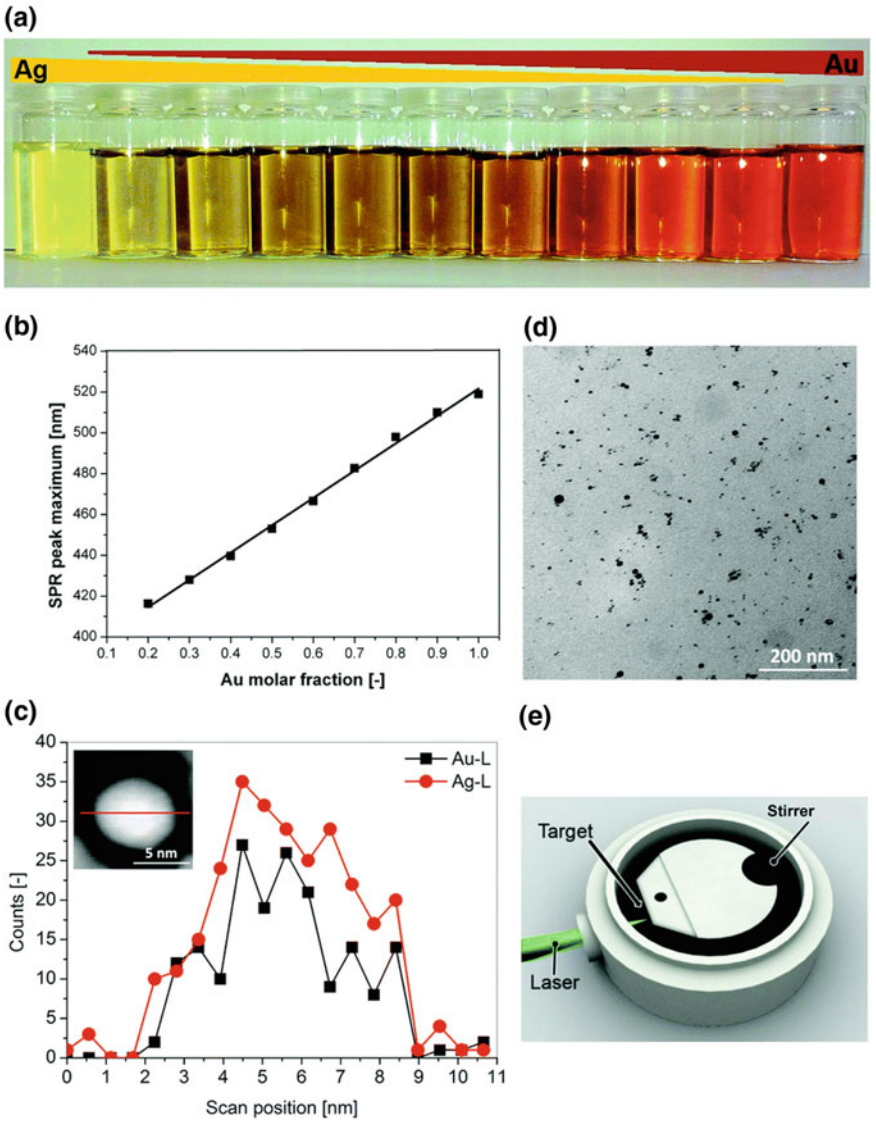

Fig. 1.7 **a** Representative AuAg nanoparticles with different molar fractions. **b** Correlation of the gold molar fraction with a maximum surface plasmon resonance extinction peak. **c** TEM-EDX line scan with an inset, showing a high-angular annular dark field micrograph. **d** TEM micrograph of Ag50Au50 nanoparticle dispersion after stabilisation with BSA. **e** Aluminum batch chamber for the synthesis of silver and gold-silver alloyed nanoparticles. (Reproduced with permission from Analyst, 2014, 139, 931–942. Copyright 2014 The Royal Society of Chemistry) [136]

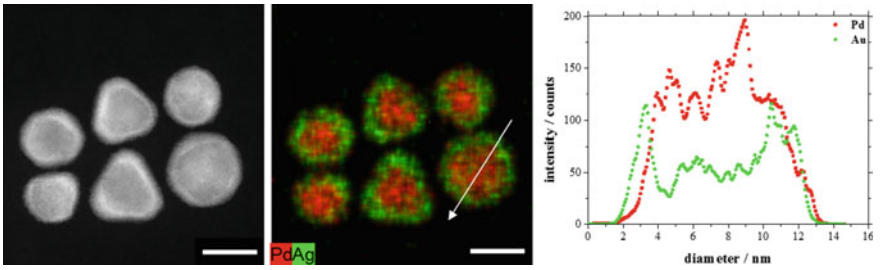

Fig. 1.8 HAADF-STEM image and corresponding EDX map with an additional line scan (white arrow) of Pd–Au core-shell nanoparticles. The EDX maps and line scans clearly show the presence of a core-shell structure with a palladium core (red) and a gold shell (green). The scale bars are 7 nm. (Reproduced with permission from ChemistrySelect 2018, 3, 4994. Copyright 2018, John Wiley and Sons)

The synthesis of alloyed nanoparticles with non-spherical morphology can lead to specific optical properties like plasmonic resonances and surface-enhanced Raman scattering (SERS) [141, 142].

1.4 Nanoscale Oxide Particles

Due to their intrinsic properties, metal oxide nanoparticles strongly contribute to a variety of applications in chemistry, physics, and materials science [143, 144]. A large diversity of oxide compounds with many structural geometries and various electronic structure (metals, semiconductors, or insulators) is known. They are widely applicable in the fabrication of sensors [145], microelectronic circuits [146], piezoelectric devices [147], fuel cells [148, 149], passivation coatings [150], water treatment agents [151], bactericides [152], sun screen [153], and as heterogeneous catalysts [154]. Almost all active phases, promoters, or "supports" in industrial catalytic reactions are based on oxides. The entanglement of size, shape, morphology, crystal structure, and surface chemistry requires a fundamental understanding and rational design for technologically relevant areas. In the following, we will discuss the prominent cases of zinc oxide, titanium dioxide (titania), and silicon dioxide (silica).

1.4.1 Zinc Oxide Nanoparticles

Zinc oxide (ZnO) is extensively utilized in everyday applications, like transparent electronics, smart windows, piezoelectric devices, chemical sensors, biosensors and dye-sensitized solar cells [155, 156]. However, zinc oxide is used at least since 2000 BC as component of therapeutic creams for skin medication [157]. Registered as safe material by the Food and Drug Administration (FDA) [158], it is used as food additive and inorganic antimicrobial additive in polymeric matrices for the packaging material, e.g. the incorporation of ZnO into the coatings of containers for meat, fish, corn and peas can retain the food color and avoid degradation [159]. Today, the commercial production of ZnO nanoparticles is realized by mechanochemical processing and physical vapor synthesis [160]. The first method is based on physical size reduction in a conventional ball mill with additives that are activated during grinding. The reaction comprises the mechanical activation of precursors ($ZnCl_2$ and Na_2CO_3) with a further thermal decomposition to ZnO [161]. The typical size range of the produced nanoparticles is 20–30 nm. The particle size can be varied by milling time and the heat treatment temperature. Physical vapor syntheses use the plasma arc energy intake by a solid precursor to generate a vapor at high temperature. Being decomposed into atoms, gases can react or condense to form particles when cooled [162].

Wet-chemical methods include hydrothermal/solvothermal processes, solution-liquid-solid, and surfactant-assisted synthesis. These methods provide a convenient and facile platform for a low-temperature fabrication of the desired ZnO nanostructures [163–165]. Typical precursors for ZnO nanocrystal preparation are zinc nitrate [166], metallic zinc [167], zinc chloride [168], zinc acetate [169, 170], and zinc sulfate [171]. If an anisotropic growth of ZnO nanoparticles is desired, surfactants such as hexamethylenetetramine [172], ammonia [173], ascorbic acid [174], and sodium hydroxide [175] can be added. Most reactions are performed at elevated temperatures up to 180 °C [165]. As shown in Fig. 1.9, different kinds of ZnO nanoparticles are obtained by adjusting the hydrolysis ratio. The nature of the protective agent added during ZnO formation and hydrolysis ratio are two major handles for size and shape control [176].

1.4.2 Titanium Dioxide Nanoparticles

Titanium dioxide nanoparticles are among the most frequently used metal oxide nanoparticles in industrial products and consumer goods [177]. Due to its very high refractive index and brightness, TiO_2 is extensively utilized as a white pigment with an annual consumption of almost four million tons worldwide [178]. Typical applications comprise paints [179, 180], coatings [181], plastics [182], papers [183], inks [184], pharmaceuticals [185], food products [186], cosmetics [187, 188], sun screens [189], and toothpaste [190]. Rompelberg et al. estimated the oral intake of TiO_2 from

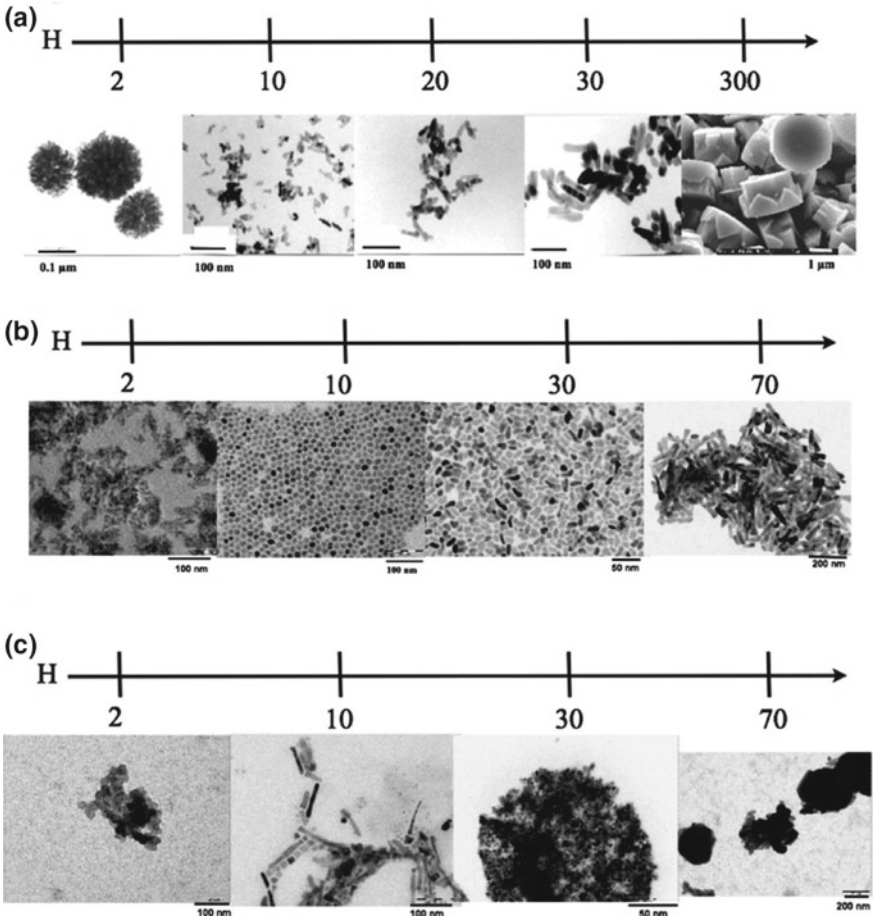

Fig. 1.9 TEM micrographs of ZnO nanoparticles synthesized in diethylene glycol (DEG) by variation of the hydrolysis ratio (*H*): **a** ZnO without addition of protective agents, **b** ZnO- tri-*n*-octylphosphine oxide, and **c** ZnO-polyoxyethylene stearyl ether. (Reproduced with permission from Langmuir 26, 9, 6522–6528. Copyright 2010 American Chemical Society) [176]

food, food supplements and toothpaste by measuring the total titanium concentrations and subsequently calculated the TiO_2 concentrations in selected representative Dutch food products (see Table 1.1) [186].

Several processes have been developed for the preparation of nanostructured TiO_2 with distinct characteristics. Commercial powders are typically prepared by the so-called chloride-process from $TiCl_4$ using hydrocarbon-assisted flame synthesis [191]. In the sulfate-process, ilmenite ($FeTiO_3$) is treated with concentrated sulfuric acid, and the titanium oxygen sulfate ($TiOSO_4$) is extracted and converted into titanium dioxide [192].

Table 1.1 Average measured total titanium concentrations and subsequently calculated TiO_2 concentrations in selected representative Dutch food products, raw (cow) milk, and food supplements. Samples rich in calcium were analyzed by ICP-HRMS, others by ICP-QMS. Limit of quantitation 0.05 mg Ti/kg product. (Reproduced from Rompelberg et al., 2016, Nanotoxicology, 10:10, 1404–1414 © 2016 National Institute for Public Health and the Environment. Published by Informa UK Limited, trading as Taylor & Francis Group) [187]

	Number of samples	Mean total-Ti (mg/kg product) (± SD)	Min total-Ti (mg/kg product)	Max total-Ti (mg/kg product)	Mean TiO_2 (mg/kg product)
Samples analysed by ICP-HRMS					
Raw (cow) milk	6 (6)	0.31(±0.23)	0.05	0.63	0.51
Regular dairy products (i.e. milk, yoghurt)	11 (10)	0.47(±0.46)	<LOQ	1.46	0.79
Processed dairy products	10 (5)	0.12(±0.17)	<LOQ	0.57	0.21
Soy milk	2 (2)	0.33(±0.01)	0.32	0.34	0.55
Dutch cake with icing and cream	1 (1)	0.23	0.23	0.23	0.38
Coffee creamer (powdered)	1 (1)	1640	1640	1640	2739
Samples analysed by ICP-QMS					
Energy drink (containing caffeine)	1 (1)	0.07	0.07	0.07	0.11
Soft drink	2 (2)	0.06 (±0.00)	0.06	0.07	0.11
Sports drink	2 (2)	0.09 (±0.05)	0.05	0.12	0.14
Syrup	2 (2)	0.17 (±0.00)	0.17	0.17	0.28
Ice (water-based)	1 (1)	0.16	0.16	0.16	0.26
Wine gums	1 (1)	0.25	0.25	0.25	0.42
Salad dressing	1 (1)	0.43	0.43	0.43	0.72
Food supplement (multivitamin)	2 (2)	744 (±1009)	31	1458	1242

The wet-chemical fabrication of TiO_2 nanoparticles allows to control the stoichiometry, homogeneity, and morphology of the resulting materials. Nevertheless, the drawbacks are expensive precursors, long processing times, the nanoparticle isolation/purification after the synthesis, and the presence of impurities. The sol-gel technique is based on the hydrolysis of the precursors of the metal alkoxides ($Ti(OR)_4$) with further thermal decomposition [193]. By controlling solution composition, pH, and temperature, the particle size can be tuned [194]. The precipitation process involves the addition of NaOH, NH_4OH, or urea to metal precursors (e.g., $TiCl_4$), followed by thermal treatment to crystallize the oxide [195]. The hydrothermal method can be started from metallic Ti, oxidized by H_2O_2 [196]. Nanocrystalline TiO_2 can be prepared by mechanical alloying from a metastable intermediate phase, i.e. $TiO(OH)_2$ powder [197]. By in-flight oxidation of titanium nitride powder in an r.f. thermal plasma reactor, the formation of core-shell structured composites (with TiN cores and oxide shells) was realized [198].

1.4.3 Silica Nanoparticles

Silicon dioxide (SiO_2) nanoparticles are extensively used since the 1950s in numerous applications like additives for rubber (also in tires) and plastics [199–201], strengthening filler for concrete [202, 203], abrasives in toothpaste [204], thickeners in foods [205], and anti-caking agents in foods (E551) [206, 207]. Due its excellent biocompatibility, low toxicity, easy surface modification, and facile synthetic routes, silica nanoparticles are suitable for biological applications as grafting platform for imaging, detecting, drug loading, and site-specific targeting [208–210]. Their particle size, crystallinity, porosity, and shape can be accurately controlled, enabling a fine-tuning of silica nanoparticles for the intended application.

The large scale production of silica nanoparticles is performed by flame aerosol technology [211]. Developed by Kloepfer [212], this fabrication method is based on the continuous flame pyrolysis of vaporized silicon tetrachloride ($SiCl_4$) [213]. The produced silica forms branched aggregates, with the primary amorphous particles in the size range from 5 to 50 nm [214]. The particle size and the particle size distribution can be modified varying the concentration of the reactants, the flame temperature, and the gas dwell time in the combustion [211].

Established in 1968, the Stöber method is a widely used sol-gel process for silica nanoparticle synthesis [215]. This reaction permits a controlled evolution of spherical silica particles of uniform size in the size range of 50 nm to 2 μm. Catalyzed by ammonia, it is based on the hydrolysis of alkyl silicates (e.g., tetraethoxysilane (TEOS)), and the subsequent condensation of silicic acid in alcoholic solutions. The control of the ratio of solvent to TEOS permits a fine control of particle size in the Stöber method [216]. As shown in Fig. 1.10, the diameter of the synthesized particle decreases as the ratio of solvent to TEOS is increased. The method can be modified for the incorporation of organic dyes and other nanosized materials [217].

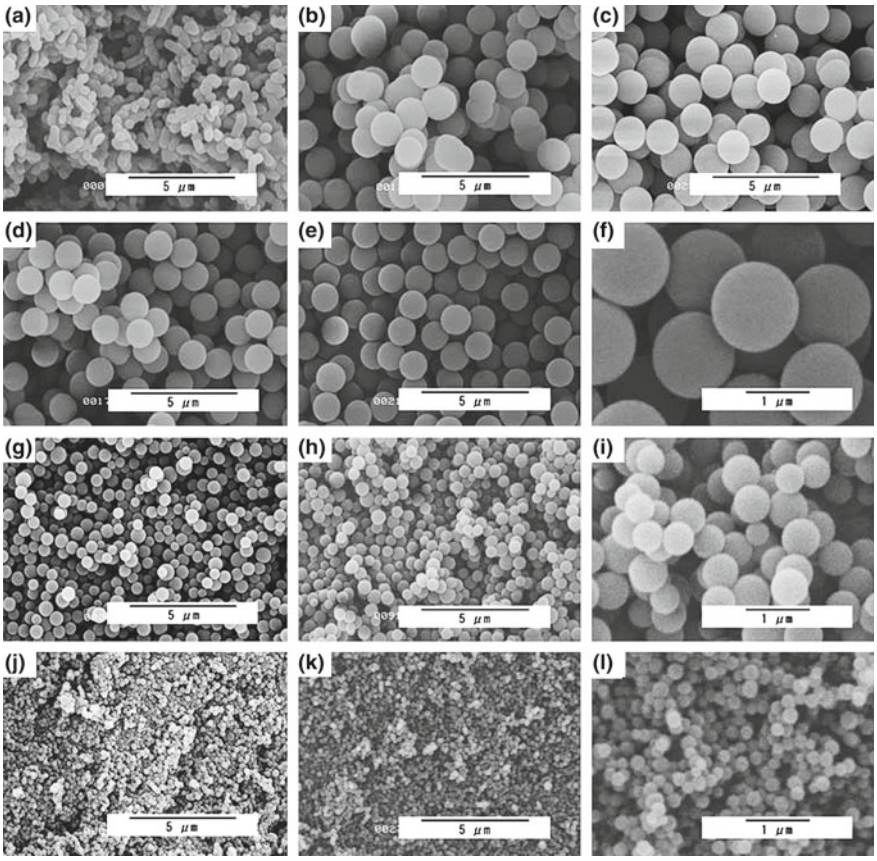

Fig. 1.10 Silica nanoparticles synthesized by the Stöber method with variable methanol/TEOS ratios before and after calcination. The MeOH/TEOS synthesis ratios and calcined versus noncalcined status are as follows: **a** 300/noncalcined, **b** 750/noncalcined, **c** 1125/noncalcined, **d** 1500/noncalcined, **e** and **f** 1500/calcined, **g** 2250/noncalcined, **h** and **i** 2250/calcined, **j** 3000/noncalcined, and **k** and **l** 3000/calcined. As the ratio of methanol/TEOS increases from 300 to 1125, the particle size increases. However, from 1125 to 6000, the particle size decreased from 1500 to 10 nm in diameter [216]. (Reproduced with permission from Shimura, N. & Ogawa, M. J Mater Sci (2007) 42:5299 Copyright © 2007, Springer Nature)

Another important technique for silica nanoparticle preparation is the reverse microemulsion. Established by Arriagada and Osseo-Asare in the early 1990s, this method utilizes the ammonia-catalyzed polymerization of tetraethoxysilane in a reverse phase (water-in-oil microemulsion) [218]. The dispersion of nanodroplets leads to nanoreactors to form nanoparticles. The size of the colloids depends on the intrinsic properties of a surfactant and the molar ratio of water to surfactant [210]. The variation of the nanoparticle morphology can drastically affect their biodistribution, bioavailability, and toxicity [219, 220]. For instance, Trewyn et al. demonstrated the

effect of organic C_n-methylimidazolium ($n = 14,16,18$) derivatives on the modified Stöber synthesis [221]. The particles derived from modifications with C18MIM and C14OCMIM exhibited a rod- or worm-like structure.

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