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Methods for chemical synthesis of colloidal gold

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Published data on the chemical synthesis of colloidal gold are summarized and systematized. Attention is focused on the state-of-the-art concepts behind the mechanisms of citrate synthesis and its control parameters, methods for fabrication of ultrafine particles (1 – 5 nm) and the control over the particle spherical shape and size in the range from 10 to 200 nm. The synthesis of gold nanoparticles in organic solvents, in particular, the two-phase Brust – Schiffrin method are discussed. The methods for obtaining gold nanoparticles with the use of synthetic and natural biopolymers that can act simultaneously as reducing agents and surface stabilizers (functional agents) are considered. The studies in which important nanomedicine drugs are used as reducing agents and ligands are analyzed.
The bibliography includes 285 references.

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1. Introduction

Mankind learned about the existence of gold back in the 5th millenium BC, in the Neolithic Age, because gold occurred in nature as a native metal. According to the assumption of archeologists, the regular production of gold started in the Middle East, from where gold ornaments were supplied, in particular, to Egypt. In China and in India, 'liquid gold' was used for medicinal purposes. In the Middle Ages, colloidal gold (CG) was reputed to be a panacea owing to its therapeutic action against various diseases. Paracelsus used the quintessence of gold (*quinta essentia auri*) as a therapetic agent, which he obtained by reduction of gold salts with ethanol or vegetable extracts in oil. He declared that chemistry was for making medicines, but not for making gold out of metals. His contemporary, Giovanni Andrea, a hieronymite, employed colloidal gold to treat some chronic diseases. The popularity of potable gold (*aurum potabile*) as a medicine is evidenced by the fact that it is mentioned in the Shakespeare's play Henry IV. The first book devoted to colloidal gold that survived until now was written in 1618 by Francisci Antonii,[1] a philosopher and a doctor, who described the preparation and medical applications of CG. In 1656, Nicholas Culpeper, an English botanist, published the treatise on *aurum potabile*, which described CG applications for medical purposes. The treatise written by David de Planis-Campy, a French alchemist, entitled 'Treatise *of the True, Unique, Great, and Universal Medicine of the Ancients, or Potabl Gold*' (1633) states that 'gold is the whole Nature, gold is the Earth seed'.[2]

Since the 17th century, owing to the works of Johann Kunckels,[3 – 5] CG was used for the production of red (ruby) glasses, painting on glasses, enamels and porcelain (using purple of Cassius, named after Andreas Cassius, a glass maker from Hamburg) and silk dyeing. The purple of Cassius was obtained by reduction of gold salts with

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stannous chloride. In 1712, Hans Heinrich Helcher[6] published a treatise about the therapeutic properties of gold, which described colloidal gold preparation and stabilization with starch; this was apparently the first example of CG stabilization with a polymer.

Scientific research into the preparation and applications of colloidal gold started in the mid-19th century. A paper by Michael Faraday[7] published in 1857 was based on his Bakerian Lecture and became the fundamental scientific work addressing methods for the synthesis and properties of CG. This paper gives the first description of CG aggregation in the presence of electrolytes, the protective effect of gelatine and other polymers, and the optical properties of thin films of dried CG. Faraday synthesized CG using white phosphorus in a CS_2 solution as the reducing agent; he paid particular attention to the quality of chemicals and purity of glassware. The CG solutions he prepared are still stored at the Royal Institution of Great Britain.

At the end of the 19th and beginning of the 20th century, several papers devoted to the properties of CG were published by Richard Zsigmondy. He described methods for the synthesis of CG with various particle size using reduction with hydrogen peroxide, formaldehyde, ethanol or white phosphorus and reported important physicochemical (in particular, optical) properties of gold sols. Curiously, while completing his fundamental paper[8] in 1898, Zsigmondy learned about Faraday's works on the same subject. Therefore, the second part of the paper, which began with apologies to the scientific community, was devoted to a thorough review of Faraday's works. Such high attention to the works of preceding researchers is rarely encountered in modern scientific publications. Furthermore, the study is amazingly thorough — subtle details of experimental results are presented, even the taste of gold sols with different particle size. In 1925, Zsigmondy was awarded the Nobel Prize in Chemistry 'for his demonstration of the heterogeneous nature of colloid solutions and for the methods he used, which have since become fundamental in modern colloid chemistry'.

Theodor Svedberg, one more Nobel Prize laureate, also carried out classical experiments on the CG preparation, analyzed CG formation mechanisms, and investigated CG sedimentation properties (using the ultracentrifuge he had invented). Svedberg studied the reduction kinetics considering more than 25 reducing agents [hydrogen, hydrogen peroxide, hydrogen sulfide, carbon monoxide, carbon disulfide, nitric oxide, phosphorus, phosphorous acid, diphosphoric acid, sulfur(IV) oxide, sodium thiosulfate, sodium hydrogen sulfate, ferrous sulfate, tin, stannous chloride, acetylene, terpenes, ethanol, glycerol, aldehydes, acrolein, oxalic acid and oxalates, tartaric acid, sugars (glucose, saccharose), starch, phenols, hydroxy acids, hydroquinone, hydrazine, hydroxylamine, denatured egg white protein] as well as α-, β- and γ-radiation; he formulated the key views about the mechanism of formation (chemical condensation) of colloidal gold particles.[9] While describing the scientific history of CG, one cannot pass over the classical publication of Gustav Mie,[10] which explains the colour of gold sol *via* solution of the problem of electromagnetic plane wave scattering by a sphere.

In the early 20th century, CG were prepared using reducing agents that are barely used now (apart from those mentioned above) such as citric and formic acid, mannitol, acetone, aromatic aldehydes, essential oils (rosemary and cinnamol oil) and many other compounds (even the aqueous extract of Dutch cigars).[11,12] The following reducing agents are still used, in some rare cases, to prepare colloidal gold: ascorbic and isoascorbic acids, disodium ethylenediaminetetraacetate (EDTA-Na_2), disodium 4,5-dihydroxybenzene-1,3-disulfonic acid (tiron), hydroquinone, tannic acid, sodium thiosulfate, sodium tartrate, ammonium hydroxide, *etc.*[13–22] Wilhelm Ostwald, the author of the colloid ripening theory, remarked[23] that in the days of alchemists, colloidal gold was prepared by reduction of gold salts by any sorts of organic compounds including urine. The ease of reduction of gold is caused by its highest electrochemical potential (+1.498 V for the Au^{3+}/Au pair); therefore, gold cations are strong oxidants.

Methods for the synthesis of CG (and other metal colloids) can be conventionally divided into two large groups depending on the type of process involved. The first group includes dispersion processes based on metal dispersion. The second group comprises condensation processes in which the reduced metal nanoparticles are formed from the ions occurring as metal salts.

A dispersion process for the preparation of CG first proposed in 1898[24] is based on destruction of the crystal lattice of gold metal under the action of high-voltage electrical current. When electric arc is generated under the action of the current in a liquid between two gold electrodes, the metal passes to the vapour state and then condenses in a dispersion medium. The use of direct current gives rise to sols with gold particles of non-uniform size. The addition of very small amounts of alkalis or chlorides and the use of high-frequency alternating current considerably improve the quality of gold hydrosols. The advantages of dispersion methods include the absence of impurities of residual chemicals in the sols (particularly on the surface of metal particles). Today, destruction of bulk samples for the preparation of gold nanoparticles is performed, most often, by laser ablation in aqueous media.[25] Benefits of this method include the environmental friendliness of the nanoparticle preparation and the absence of any foreign impurities in the suspension. The drawbacks of the method are broad particle size distribution and the lack of control over the particle shape.

The second, more popular, group of methods is based on the synthesis of colloidal particles from gold halides using chemical reducing agents and/or irradiation (ultrasonic, ultraviolet, high-frequency radiation, pulse or laser radiolysis, γ-radiation).[26]

A relatively new trend of nanobiotechnology is CG synthesis by green chemistry techniques using cells or waste products of plants, microbes and animals.[27,28] It is noteworthy that alchemists prepared CG exactly by green synthesis. However, the nanoparticles obtained in this way usually have fairly broad size and shape distributions.

In the early and mid-20th century, scientists used CG to study the optical properties of metal particles and clusters and mechanisms of aggregation and stabilization of colloids, and also in analytical chemistry and geobiochemistry. In medicine, the most popular application of CG is the Lange reaction, a colour reaction based on CG coagulation on exposure to substances that are present in the cerebrospinal fluid in pathological states.[29]

Despite the many-century history of CG, the 'revolution in immunochemistry'[30] related to the application of gold particles in biological studies occurred only in 1971 when

W. Page Faulk and G. Malcolm Taylor [31] reported a protocol for antibody conjugation to colloidal gold for direct electron microscopy visualization of the surface antigens of salmonellae. Thus, a CG conjugate with immunoglobulins was first used as an immunochemical marker. This marked the beginning of active use of specific biomarkers — CG conjugates — in various fields of biology and medicine. An enormous number of papers devoted to application of functionalized nanoparticles — conjugates with recognizing biomacromolecules (antibodies, lectins, enzymes, aptamers, *etc.*) [32, 33] was published by biochemists, microbiologists, immunologists, cytologists, plant physiologists, morphologists and other professionals. Apart from traditionally used transmission electron microscopy, CG started to be widely investigated by scanning electron microscopy, optical microscopy, various types of probe microscopy and solid-phase techniques (dot blot analysis and immunochromato-

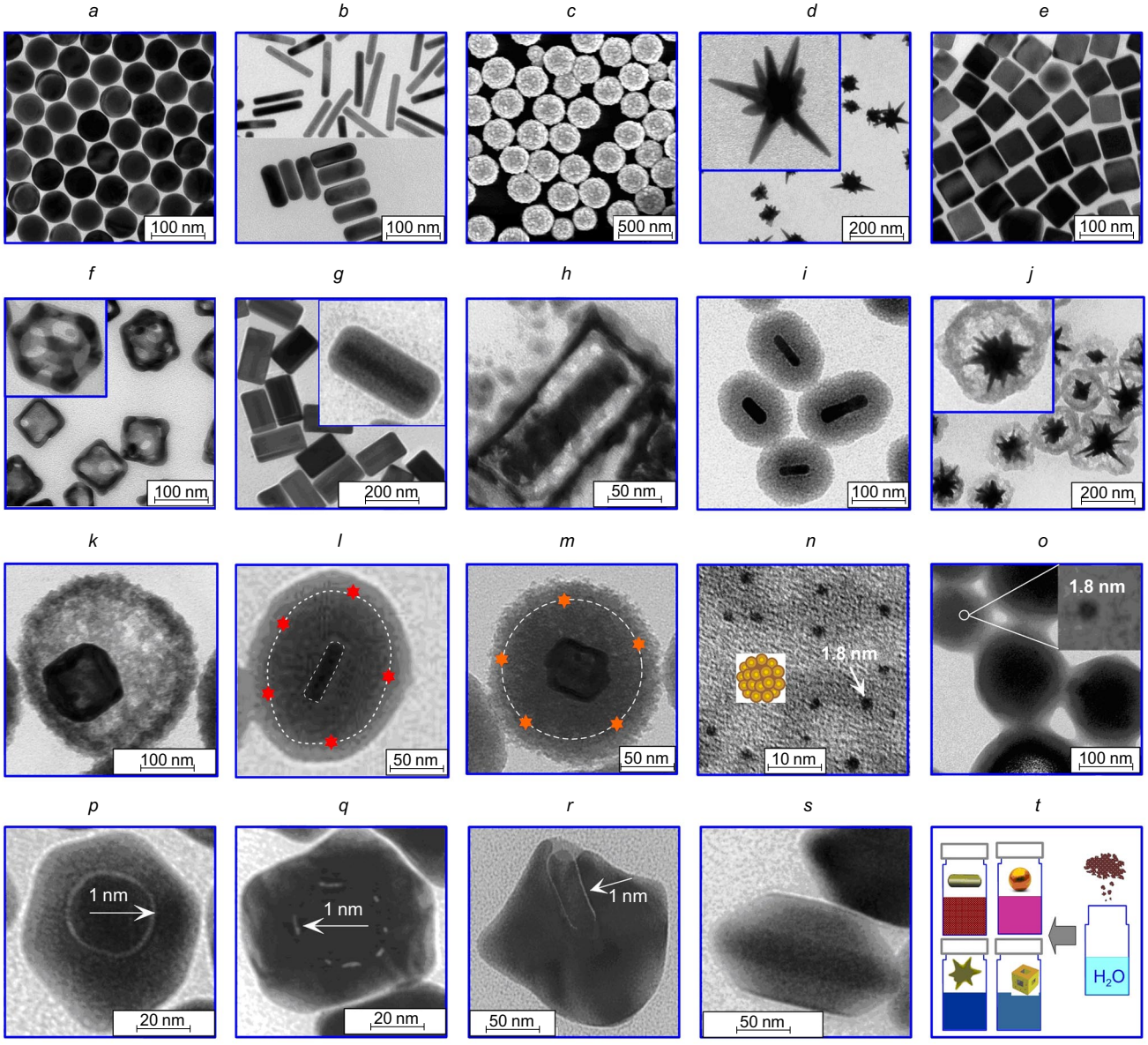


Figure 1. TEM gallery of images of nanoparticles and nanocomposites synthesized at the Laboratory of Nanobiotechnology, IBPPM RAS: gold nanospheres (*a*); gold nanorods (*b*); gold nanoshells on silica cores (*c*); gold nanostars (*d*); silver nanocubes (*e*) used as templates for the synthesis of gold nanocages (*f*); nanocuboids composed of gold nanorods coated by a silver shell (*g*); anisotropic gold nanocages obtained from nanocuboids (*h*); gold nanorods (*i*), nanostars (*j*) and nanocages (*k*) coated by a mesoporous silica shell; gold nanorods (*l*) and nanocages (*m*) coated by a conventional and mesoporous silica shell and doped with photodynamic agents; fluorescent atomic gold nanoclusters Au_{25} stabilized by bovine serum albumin (BSA) molecules (*n*); human serum albumin (HSA) nanoparticles doped with fluorescent atomic clusters (*o*); surface enhanced Raman scattering (SERS) gold labels with benzene-1,4-dithiol molecules embedded into a nanometre hollow (*p*) or bridged (*q*) gap between the spherical (*p*) or polygonal (*q*) core and the shell; anisotropic labels with a gold nanorod as the core and benzene-1,4-dithiol or nitrobenzene-1,4-dithiol embedded into the 1-nm gap between the core and the gold shell (*r*); SERS labels based on gold nanorods functionalized by 4-aminothiophenol and 4-nitrobenzenethiol molecules coated by a silver shell (*s*); water-soluble powders of gold nanospheres, nanorods, nanostars and nanocages (*t*) (powder particles coated by thiolated mPEG-SH molecules, $M_w = 5000$).[35, 45–56]

graphic test systems), sol particle assay, quantitative protein determination, *etc.*[34–36]

The second surge of interest in CG (now in gold nanoparticles) is associated with vigorous development of technologies at the turn of the 21st century. This is due to the fact that the unique physicochemical properties of gold nanoparticles depending on their size, shape and composition have found wide use in various fields of modern science: nanomedicine, nanoelectronics, nanocatalysis, nanophotonics, nanoplasmonics and nanosensorics.[37–40] Methods for large-scale synthesis of various nanoparticles, in particular, gold nanoparticles, have been surveyed.[41] It is noteworthy that apart from conventional CG composed on quasi-spherical particles (nanospheres), other shapes such as nanorods, nanoshells, nanocages, nanostars, nanoplates and nanoclusters and also gold nanocomposites are now used; procedures for the preparation of these particles are described in detail in reviews.[42–44] As an example, consider the gallery of images of nanoparticles obtained at the Laboratory of Nanobiotechnology of the IBPPM RAS (Fig. 1).[35,45–56]

This review covers only condensation syntheses of spherical gold nanoparticles in solutions using chemical reduction. Despite the availability of procedures for the synthesis of gold nanoparticles with a variety of shapes and structures, spherical nanoparticles of various sizes are still most popular in many fields of fundamental science and practice.

The following abbreviations are used:
AuNP — gold nanoparticles,
BSA — bovine serum albumin,
CG — colloidal gold,
CTAC — cetyltrimethylammonium chloride,
EDTA — ethylenediaminetetraacetic acid,
HSA — human serum albumin,
PEG — polyethylene glycol,
PEI — polyethyleneimine,
PVP — polyvinylpyrrolidone,
SEM — scanning electron microscopy,
SERS — surface enhanced Raman scattering,
TEM — transmission electron microscopy.

2. Citrate synthesis of colloidal gold

Currently, citrate synthesis is the most popular approach for the preparation of gold nanospheres with a specified particle size in the 15–150 nm range. The synthesis of CG with sodium citrate being used as the reducing agent is called in the literature either Turkevich method,[57] or Frens method,[58] or, in some cases, Turkevich–Frens method. However, it would be fair to call it the Borowskaja method, because Borowskaja was the first to propose sodium citrate as the reducing agent for the preparation of CG (in 1934),[59] while the paper by Turkevich *et al.*[57] was published in 1951 and the paper by Frens[58] appeared in 1973.

The CG preparation procedure proposed by Borowskaja is described as follows: pour 95 ml of distilled water into a clean, thoroughly washed, dry flask, add 1 ml of 1% chloroauric acid ($HAuCl_4$), heat the flask to 95 °C, add 5 ml of a 1% solution of sodium citrate to the hot solution and heat nearly to boiling. If the preparation is correct, the addition of sodium citrate is followed by fast appearance of temporary blue colour, which gradually changes to red. The whole preparation process lasts for 1–3 min. It is important to exactly follow the order of reactant addition: simultaneous addition of $HAuCl_4$ and the citrate gives coarsely dispersed, poorly stable solutions. A properly prepared solution is applicable for 2–3 months. According to our estimates, the diameter of CG particles obtained by Borowskaja was 15–20 nm.

Borowskaja proposed this procedure for CG synthesis with the goal to perform the Lange reaction. This procedure was used rather widely in 1940s;[60–63] in particular, it was recommended by Carl Lange, founder of the diagnostic method,[64,65] who had previously prepared CG using formaldehyde.

In 1951, John Turkevich *et al.*[57] published a fundamental study devoted to particle nucleation and growth processes during the synthesis of CG. The authors focused attention on the citrate synthesis. The procedure of citrate synthesis was virtually identical to the Borowskaja procedure. According to transmission electron microscopy (TEM) examination of 1046 particles, their average diameter was 20 ± 1.5 nm and the root-mean-square deviation was 12.5%. The authors noted that these results were obtained when the growth solution was heated to 100 °C. When the reaction mixture was maintained at 80 °C, the average particle diameter was 16.5 nm; and at 70 °C, it was 18 nm. At lower temperature, the time required for sol formation increased from 5 to 45 min.

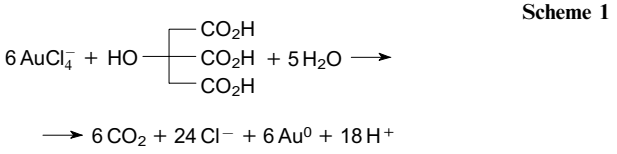
According to TEM data, the spherical particles of colloidal gold obtained by the citrate method were more uniform in shape and size than the particles prepared with other reducing agents (white phosphorus, acetone, tannin, oxalic acid, hydroxylamine, carbon monoxide, acetylene, citric acid). In addition, the authors demonstrated that a change in the ratio of $HAuCl_4$ to sodium citrate amounts in the reaction mixture changes the size of the particles.

Using TEM, Siedentopf–Zsigmondy ultramicroscopy and nephelopmetry, nucleation curves were measured during the citrate synthesis. At 23 °C, the nucleation time was 40 min, and at 58.5 °C, it was 4 min, which was indicative of the strong temperature dependence of the nucleation process. The nucleation rate was approximately constant in the beginning and sharply decreased at the end. The formation of nuclei was completed well before the CG formation: the typical red colour of the solution appeared after 12 h at 23 °C or after 2 h at 58.5 °C. Analysis of the nucleation curves revealed four regions, namely, the induction period, which was followed by fast growth in the beginning of nucleation, a linear segment and, finally, the degradation region. The overall shape of the curve is characteristic of an autocatalytic reaction. The particle growth process is a typical heterogeneous reaction.

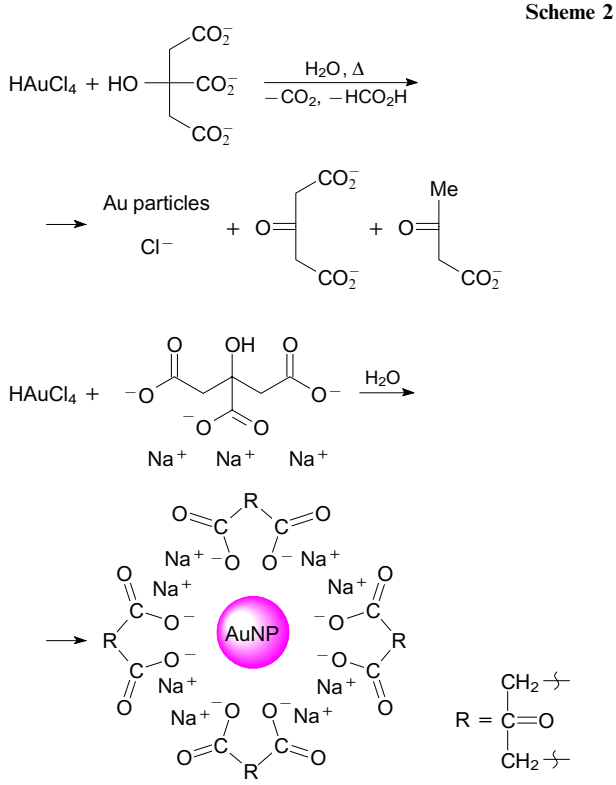
The authors also demonstrated[57] that the citrate synthesis of CG in solutions involves the formation of intermediate products, in particular, acetonedicarboxylic (β-ketoglutaric) acid. Other possible intermediates of the citrate synthesis are formate and oxalate ions.[66]

The reaction involved in the citrate synthesis is shown in Scheme 1.[67]

Scheme 1



Scheme 2



Mirkin[66] proposed a somewhat different pathway of oxidation of citrate and dicarboxylate ions (Scheme 2, upper reaction). The general pattern of formation of gold particles stabilized by citrate ions is shown in Scheme 2 (lower reaction).[26]

Most methods used for CG preparation by chemical reduction are based on the condensation reaction from a supersaturated solution of $HAuCl_4$. Zsigmondy and Svedberg[8,9] investigated the reduction kinetics and formulated the basic views on the mechanism of formation of gold particles considering reduction of $HAuCl_4$ with hydrogen peroxide. According to Zsigmondy's interpretation, the variation of the electrical conductivity of the reaction mixture reflects the following processes. First, reduction of approximately 30% of $HAuCl_4$ takes place. This gives a highly (approximately sixfold) supersaturated gold solution. Then the reduction is sharply retarded and gold condensation giving tiny particles (nuclei of the new phase) takes place. The particles can form large, but unstable aggregates, which is usually termed as 'coagulation'. As this takes place, the sol assumes a blue colour. The aggregated particles gradually become larger and, as large aggregates degrade, they become the centres for further fast reduction. When the nuclei attain a certain critical size, a stable, red-coloured sol is formed (Fig. 2). It has been shown[68–73] that a similar mechanism for the formation of gold nanoparticles is involved in the citrate synthesis. Detailed information about the mechanisms of nucleation and growth of gold nanoparticles can be found in experimental papers and reviews.[74–79]

The version of the citrate method proposed by Frens[58] implies the addition of a 1% aqueous solution of sodium citrate to a boiling 0.01% $HAuCl_4$ aqueous solution, with the amount of sodium citrate being varied depending on the desired particle size. The adjustment of concentrations for the formation of particles with a specified size distinguishes this procedure from the analogues using sodium citrate as the reducing agent. While taking a constant amount of $HAuCl_4$ for the preparation of 50 ml of a suspension of gold particles of various sizes, Frens added 1.0, 0.75, 0.5, 0.3, 0.21 or 0.16 ml of a 1% sodium citrate solution. Thus, the molar ratio of the reactants decreased from 2.7 to 0.4. The average diameters of the synthesized CG particles were 16, 24.5, 41, 71.5, 97.5 and 147 nm, respectively. The absorbance of the resulting sols was in the range of 0.8–1.2. After formation of gold particles (15 min), the addition of new portions of the reducing agent did not induce noticeable optical changes. The gold concentration was constant and equal to 57 μg ml^{-1} (2.85×10^{-4} mol litre^{-1}). An increase or decrease of the molar ratio relative to the optimal range (0.75–1.35) resulted in a lower reaction rate and formation of larger particles.[80]

Smaller gold nanoparticles (8–10 nm) are prepared by a procedure of citrate synthesis differing in the order of reactant addition: sodium citrate is added first and $HAuCl_4$ is added after that.[81] It was shown that the reverse order of reactant addition gives more homogeneous finely dispersed sols.[82,83] In some cases, the citrate method is modified to prepare CG with equivalent absorbance $A_{520} \approx 2.5$ and particle diameter of 13 nm.[84] The effect of reactant concentrations and ratio on the final particle size was studied in sufficient detail,[85,86] and it was found that the particle diameter of 8–10 nm is the lower limit for this procedure.

Unlike Frens, who empirically selected the concentrations of the reducing agent, Khlebtsov *et al.*[87] plotted a calibration curve for calculating the appropriate amount of

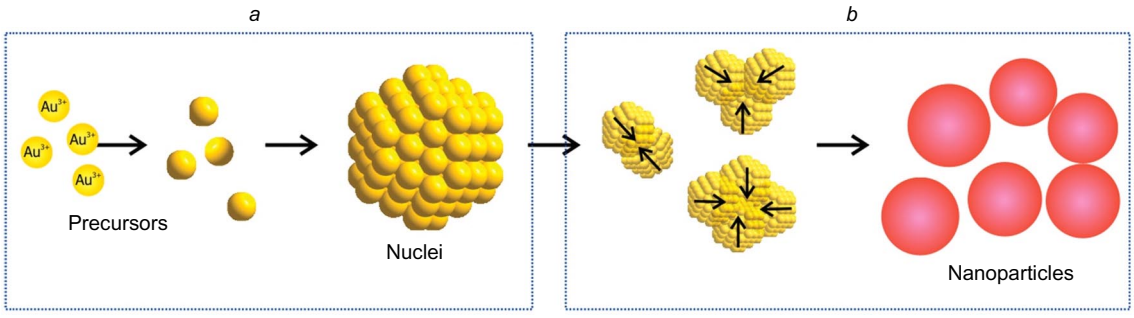


Figure 2. Scheme of formation of gold nanoparticles:[71] (*a*) reduction and nucleation, (*b*) coalescence of the nuclei.

sodium citrate for the synthesis of gold particles of a desired size using a 0.01% $HAuCl_4$ solution. The equation of the approximation curve has the form

$$d = 38.2\ V^{-0.855} \quad (1)$$

where V is the volume (ml) of a 1% sodium citrate solution per 100 ml of the sol, d is the average CG particle diameter (nm).

According to spectrophotometric and TEM studies, the higher the rate of sodium citrate addition, the smaller the average diameter and the more narrow the size distribution of the resulting gold particles.[88]

Turkevich's data about the effect of temperature on the CG particle size were supported by Rohiman *et al.*:[89] raising the temperature of synthesis resulted in smaller nanoparticles and shorter time required to reach the activation energy during the reduction. The reaction temperature can serve as an additional parameter for correcting the nanoparticle growth rate during the reduction of $HAuCl_4$ with sodium citrate.[90] The Turkevich method can also be implemented at room temperature (at pH 5.0), but the synthesis time increases in this case to 24–48 h.[91,92]

Kumar *et al.*[93] proposed a theoretical model for the mechanism of citrate synthesis. The particles are formed *via* the following sequence of stages: Au^{3+} reduction in solution to Au^{+}; disproportionation of Au^{+} to give Au atoms; Au nucleation; particle growth as a result of disproportionation on the surface; and coagulation. The oxidation of the citrate affords dicarboxyacetone, which facilitates nucleation, but also decomposes to give by-products. These stages served as the basis for a detailed kinetic model to predict the particle size distribution. Unlike conventional processes in which the particle size is dictated by balance between the nucleation and growth, according to this model, the particle size in the citrate process is determined by the balance between the nucleation and dicarboxyacetone degradation rate. This peculiarity accounts for the unusual dependence of the average particle size on the ratio of sodium citrate and gold chloride concentrations. It was also found that coagulation is an important factor for the control of particle size at high citrate concentrations.

Subsequently it was shown that the critical role in the variation of the nanoparticle size in the citrate synthesis belongs to the solution pH, which is determined by the ratio of sodium citrate and $HAuCl_4$ concentrations.[94] Two considerably different reaction pathways were identified with the switch point at pH 6.2–6.5. When pH >6.2, highly reactive $[AuCl_3(OH)]^-$ is converted to less reactive $[AuCl_2(OH)_2]^-$ and $[AuCl(OH)_3]^-$. It was demonstrated[95] that a broad particle size distribution is obtained when pH is below 5.0, with the particles being ellipsoidal and the diameter of these particles being usually >40 nm. A narrow size distribution of nearly spherical particles is obtained at pH >6.0. A mixture of ellipsoidal and other shapes with aspect ratios more than unity is formed when the reaction is carried out at pH values in the 5.0–6.0 range. The appearance of ellipsoidal and rod-like particles was attributed[96] to decreasing concentration of sodium citrate. The pH values of the reaction mixture can be controlled not only *via* the $HAuCl_4$ to citrate concentration ratio, but also by adding sodium hydroxide to the solution at certain time intervals; this makes it possible to obtain gold nanoparticles 6–15 nm in diameter.[97] A modification of the citrate method for CG synthesis involving addition of NaOH to the reaction mixture and temperature control was reported.[98] It was ascertained that the addition of an optimal amount of NaOH (5.3–6.6 mmol litre^{-1}) gives rise to uniform spherical nanoparticles with a narrow size distribution. Low reaction temperature enabled control over the rate of nanoparticle formation; the energy saving at the stage of heating was >90%.

The data on the pH effect on the outcome of citrate synthesis were confirmed by NMR spectroscopy[99] and molecular[100] and mathematical[101] modelling.

Thus, the key control parameters of citrate synthesis are the $HAuCl_4$ to citrate concentration ratio,[102] pH of the reaction mixture, reaction temperature and duration, and the order of addition of the reactants.[103]

3. Modifications of the citrate synthesis

Currently, quite a number of modifications for the classical citrate synthesis of CG have been developed. They are directed, first of all, towards expansion of the range of sizes of the resulting nanoparticles and towards formation of particles of more uniform size and shape. As a rule, these results are attained by introduction of additional reagents, which improve characteristics of the target nanoparticles, by variation of pH of the medium and reaction temperature and by using physical methods to initiate the synthesis.

For example, the use of ultraviolet radiation instead of heating for the preparation of nanoparticles by the citrate process gave particles of spherical shape even though the particle size was large.[104] A similar result was obtained by addition of trace amounts of Ag^{+} ions to the reaction mixture.[105] The use of α-hydroxycarboxylate anions instead of citrate ions was proposed.[106] The structure and the primary oxidation product of these ions had a considerable effect on the shape, size and size distribution of the gold nanoparticles. The position of the hydroxy group relative to the carboxyl was a crucial factor for the reduction efficiency.

Shulz *et al.*[107] described simple ways of successful modification of the classical citrate synthesis. Gold nanoparticles prepared by the optimized protocol had a much more narrow size distribution (standard deviation of 5%–8%). The key features of the improved protocol include control of the pH using the citrate buffer, instead of a citrate solution, for the reduction and optimization of the order of reactant addition. Also, the uniformity of particle shape can be improved by adding 0.02 mmol litre^{-1} of EDTA-Na_2.

In some versions of the citrate process, pre-synthesized nuclei are introduced into the reaction medium and then serve as the centres of condensation.[108] The possible reducing agents applied for the synthesis of small nuclei (5 nm) include hydroxylamine,[109,110] sodium borohydride[111] and tannic acid;[112] for the preparation of larger particles (10–15 nm), ascorbic acid[113] or sodium citrate[91,114] can be used. According to the cited authors, the large particles (50–300 nm) thus formed had a much more narrow size distribution (Fig. 3). The major requirement to the reaction conditions that would ensure the preparation of monodisperse and isomorphic sols is preventing the formation of new nuclei. As a rule, this is attained by a gradual increase in the gold concentration in a medium containing ripened metal sol particles and by control of the temperature and

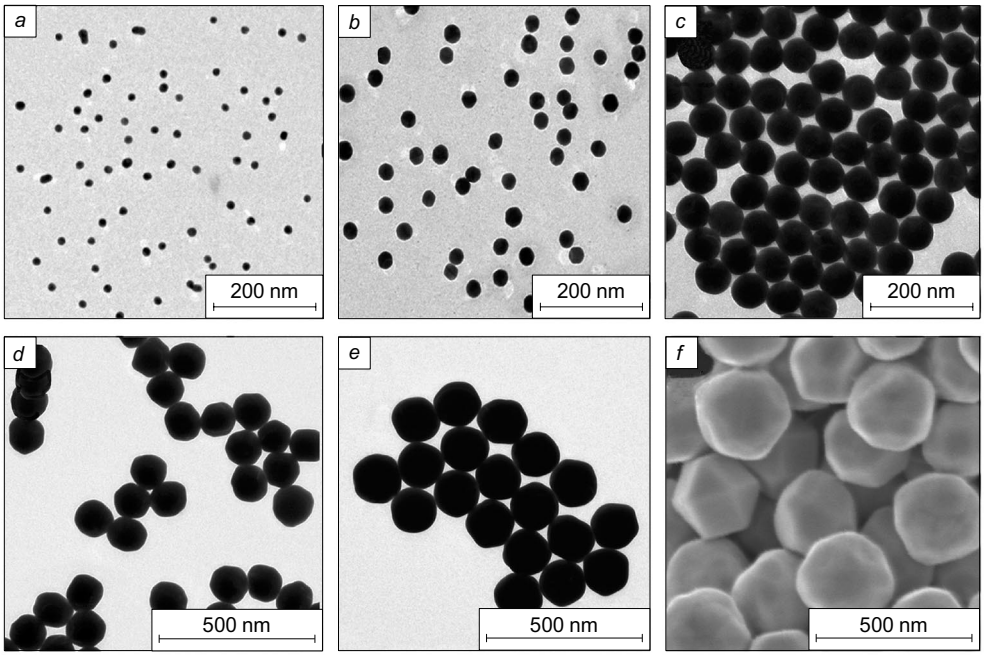


Figure 3. TEM images of colloidal gold particles with diameters of 15 ± 2 (nuclei, *a*), 31 ± 3 (*b*), 69 ± 3 (*c*), 121 ± 10 (*d*), 151 ± 8 nm (*e*) and SEM image of 294 ± 17 nm nanoparticles (*f*).[113]

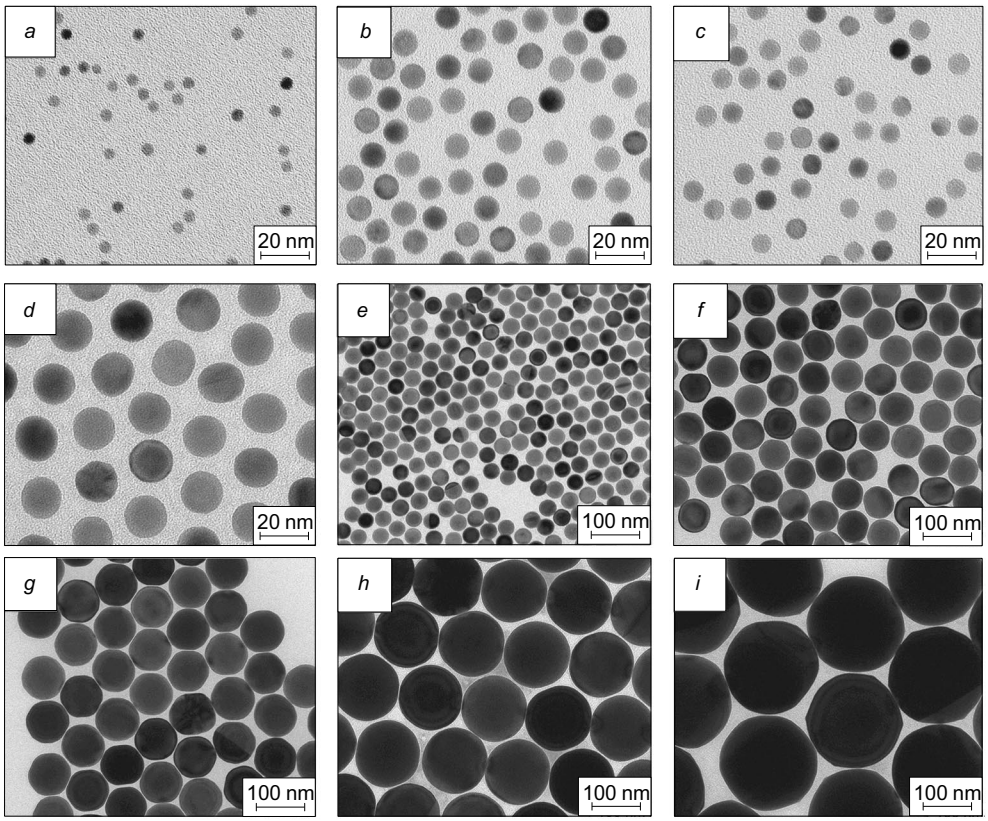


Figure 4. TEM images of gold nanoparticles stabilized by cetyltrimethylammonium chloride (CTAC) with diameters of 5 (*a*), 8 (*b*), 10 (*c*), 16 (*d*), 23 (*e*), 46 (*f*), 70 (*g*), 100 (*h*) and 150 nm (*i*).[121]

pH.[114,115] Along with sodium citrate, other reducing agents can be used such as hydroquinone,[116,117] hydrogen peroxide,[118] sodium acetylacetonate [119] and tris(hydroxymethyl)-aminomethane.[120]

A method has been developed for the synthesis of uniform single-crystalline gold nanospheres 5–150 nm in diameter by the nucleation method in a medium containing cetyltrimethylammonium chloride micelles with ascorbic acid as the reducing agent.[121] Figure 4 illustrates the high quality of nanoparticles obtained by this method. A drawback of this method is long duration of the synthesis (1 h) of particles >15 nm in diameter, since 2 ml of $HAuCl_4$ is added at a rate of 2 ml h^{-1} with a syringe pump. Note that this procedure characterized by a very low rate of addition of the reducing agent is in sharp contrast with the procedure [100] in which fast addition is recommended. Apparently, this difference is attributable to different chemical compositions of the reaction solution.

4. Preparation of gold nanoparticles less than 5 nm in diameter

The synthesis of virtually monodisperse sols with diameter *d* of about 3–5 nm was a challenge, which was not solved by the citrate synthesis of colloidal gold. In the 19th century, white phosphorus was used as the reducing agent to prepare particles with diameters of 3 nm. A drawback of this method is high toxicity and self-ignition of white phosphorus; this makes this method hardly applicable in a conventional laboratory.

For the synthesis of ultrasmall particles 2–3 nm in diameter, reduction with sodium or potassium thiocyanate is used most often.[122,123] The final nanoparticles are capable of conjugation with biospecific probes and can be used in immunocyto- and histochemical investigation methods. More rarely, ultrasmall particles are prepared using triphenylphosphine [124] or tetrakis(hydroxymethyl)phosphonium chloride.[125]

In the 1980s, a method based on simultaneous use of sodium citrate and tannic acid as reducing agents in a refluxing solution was proposed for the preparation of nanoparticles with diameters of 3–8 nm.[126,127] However, this method has not found wide use because of poor quality of the biomarker prepared with this CG due to adsorption of tannic acid and polymeric products of its oxidation on the colloidal gold particles; this resulted in experimental complications in the stage of conjugation of gold particles with a biospecific probe.

Sodium borohydride is employed most often for reduction in the synthesis of gold nanoparticles with a 5 nm diameter in aqueous solutions. It is rarely used as the only reducing agent,[128–130] more often, in combination with sodium citrate,[131] EDTA-Na_2 (Ref. 132) or hydroxylamine.[133] The reduction with sodium borohydride is conducted at room temperature with vigorous stirring using an ice-cooled solution of sodium borohydride. The reduction occurs almost instantaneously. Sols obtained in this way are distinguished by high stability and, according to TEM data, they are virtually monodisperse. More rarely, sodium cyanoborohydride is employed for CG synthesis.[134]

5. Preparation of gold nanoparticles in nonaqueous media. Brust–Schiffrin method

All of the methods for CG synthesis described above implied the reduction of gold in aqueous medium. However, for some applications, for example, for the use as additives to liquid crystalline systems, aqueous sols are unsuitable. Among the methods developed for CG synthesis, there are processes conducted in organic solvents such as ethanol, methanol, n-hexane, cyclohexane, n-heptane, toluene, tetrahydrofuran, ethylene glycol, dimethylformamide and so on.[135] Both the solvents themselves (ethanol, methanol) and other compounds such as hydrazine, acetone, *etc.*, can serve as the reducing agents. Sols obtained in organic solvents are, most often, polydisperse and unstable. Therefore, stabilizing agents, for example, polyvinylpyrrolidone (PVP), are often added to the reaction mixture. In addition, so-called two-phase (microemulsion) method is used to prepare gold nanoparticles. In the first stage, metal-containing reagents are transferred from the aqueous phase to an organic solution, to which solutions of surfactants and reducing agents are then added. This process was found to give virtually monodisperse sols.[136,137] Subsequently, a one-phase protocol was developed, according to which a surfactant and a reducing agent were added simultaneously to a metal-containing organic solution.[135] Since it was found that a strong donor-acceptor (semipolar) bond is formed between the sulfur and gold atoms,[138] alkanethiols, which form dense self-assembled monolayers on the gold surface, were added to the reaction solution.[139]

In 1994, Brust *et al.*[140] proposed a new process for the preparation of gold nanoparticles in a two-phase system, which was called the Brust–Schiffrin method and became fairly popular in recent years. This is a two-phase synthesis involving a thiol ligand, which is strongly bound to gold. The $AuCl_4^-$ ion is transferred from the aqueous phase to toluene by means of the tetraoctylammonium bromide as a phase transfer agent and is then reduced with sodium borohydride in the presence of dodecanethiol to give exceptionally stable self-assembled monolayers on the nanoparticle surface. Kinetically, the process is limited by two factors: the interfacial area and the phase transfer rate. The average size of nanoparticles thus formed is 1–3 nm. This process easily gives gold nanoparticles of controlled size, low polydispersity and high aggregative stability against changes in the temperature and ionic strength of the solution. The nanoparticles can be precipitated and redispersed in water without irreversible aggregation.

The reaction is depicted in Scheme 3.[140]

Scheme 3

$$AuCl_4^- + N(C_8H_{17})_4^+(PhMe) \longrightarrow$$
$$\longrightarrow N(C_8H_{17})_4^+AuCl_4^-(PhMe)$$
$$m\,AuCl_4^-(PhMe) + n\,C_{12}H_{25}SH(PhMe) + 3m\,e^- \longrightarrow$$
$$\longrightarrow 4m\,Cl^- + (Au_m)(C_{12}H_{25}SH)_n(PhMe)$$

The source of electrons is BH_4^-.

The mechanism of growth of gold nanoparticles by the Brust–Schiffrin method is described in detail by Perala and

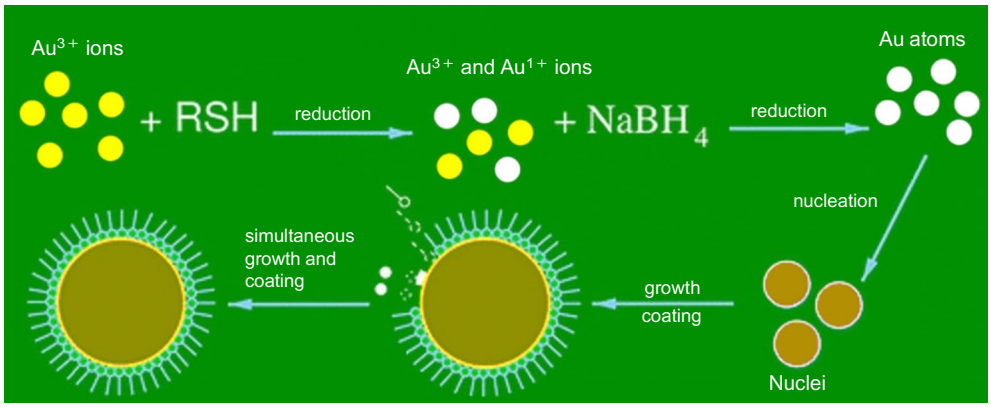


Figure 5. Scheme of the synthesis of gold nanoparticles coated by the thio ligand according to the Brust–Schiffrin.[141]

Kumar.[141] It was found that under invariable conditions of synthesis, the continuous nucleation–growth process leads to complete coating of equally sized particles by a thio ligand, which prevents further particle growth (Fig. 5).

The Brust–Schiffrin method was modified for the preparation of large gold nanoparticles with a diameter of 15–40 nm; modification included a change in the reactant ratio or the use of nuclei.[142, 143] It was also shown that some compounds such as alkanethiols, amines, silanes, phoshines, halides and simple alkanes are able to act as stabilizing agents in the digestive ripening, that is, the process in which a colloid solution is converted from a polydisperse to nearly monodisperse system on refluxing in a solvent (most often, acetone, toluene or *tert*-butyltoluene) in an argon atmosphere.[144] The digestive ripening involves the degradation (breaking) of large metal nanoparticles upon heating the suspension to a temperature close to the boiling point in the presence of alkanethiols (or other ligands) and formation of new monodisperse particles.[145]

6. Synthesis of gold nanoparticles with the use of synthetic polymers

The traditional production of specific biomarkers, CG conjugates, consists in the synthesis of gold nanoparticles by the reduction of chloroaurates with low-molecular-mass compounds and the subsequent adsorption of biopolymers on the particles. Much more rarely, gold nanoparticles are synthesized in the presence of synthetic polymers such as polyacrylamide (reduction with sodium borohydride),[146] PVP (reduction with potassium bitartrate, ascorbic acid, sodium diphenylaminosulfonate, sodium borohydride or sodium citrate),[147–151] styrene–vinylpyridine copolymer (reduction with hydrazine),[152] polyethylene glycol (PEG) (reduction with hydroxylamine),[153] polyethyleneimine (PEI) or poly(vinyl alcohol) (reduction with sodium borohydride or ascorbic acid). Mayer and Mark [154] employed 15 homopolymers and copolymers added to the reaction mixture for the reduction of $HAuCl_4$ with sodium borohydride or on exposure to ultraviolet radiation. The authors noted that the particles formed in this way were distinguished by high uniformity of size and shape. In addition, after the formation, they already had a protective polymer coating. Apart from synthetic polymers, high-molecular-mass surfactants, in particular, cetyltrimethylammonium bromide, are used for CG synthesis (reduction with ascorbic acid).[155–158]

A number of researchers proposed using polymers in the CG synthesis as simultaneously reducing agents and stabilizers. The gold particles thus formed also had a protective polymer coating. Polyethylene glycol and poly(vinyl alcohol) were used for the first time as the reducing polymers.[159] The reduction was carried out at room temperature with vigorous stirring. In the case of PEG with $M_w = 20\,000$, the solution colour changed after 8 min, and the process was completed in 8 h. During the reduction of $HAuCl_4$ in the presence of PEG, the reaction mixture first assumed a pale pink colour, which then turned into bright red (*i.e.*, no blue colouring corresponding to reversible aggregation of small particles was observed). Hence, the mechanism of formation of the gold sols seems to differ from the classical mechanism. The stability of the obtained gold colloids and the rate of reduction depended on the polymer molecular mass: PEG 20 000 > PEG 8000 > PEG 3350 > PEG 1450. Poly(vinyl alcohol) proved to be a less efficient reducing agent than PEG.

Polyethylene glycol was employed as a single reducing agent to prepare gold nanoparticles 15–20 nm in diameter. The reduction was initiated by ultrasonic treatment.[160] As in the case of sodium citrate, in the PEG-induced reduction, the addition of NaOH to the reaction mixture affects the size of the target particles.[161]

The activity of PEI as the reducing agent for $HAuCl_4$ proved to be markedly higher compared to PEG and PVP.[162] The reduction was carried out under reflux with vigorous stirring. A spectrophotometric study was performed for the first time to compare the kinetics of formation of gold sols upon the reduction of $HAuCl_4$ by two chemically different compounds, sodium citrate and PEI. The measurement of the spectra started as the temperature of the mixture reached 90 °C and was repeated at equal time intervals (1 min). Considerable differences were detected in the reduction rate (which was relatively high for sodium citrate and substantially lower for PEI) and in the spectral characteristics of the resulting sols.

In both cases, the initial stages of the reaction were accompanied by a decrease in the absorbance in the short-wavelength part of the spectrum (at the characteristic point of the absorption spectrum at $\lambda = 320$ nm), which was caused by decreasing concentration of gold existing in the

ionic form. The absorbance in the 500–550 nm range characteristic of gold sols was insignificant. However, the subsequent $HAuCl_4$ reduction kinetics were considerably different in these cases. When sodium citrate was used, the absorbance in the long-wavelength region sharply increased, with the absorption maximum gradually shifting from 700 to 520 nm. In the case of PEI, appearance of an additional absorption band was not detected, but a smooth increase in absorbance with a peak at 520 nm took place. The solution colour first became pale-pink and by the end of the reduction (30 min), it was bright red.[162]

The detected differences between the absorption spectra and their time variation for the use of two above-indicated reagents can be explained considering the theory of $HAuCl_4$ reduction according to the Zsigmondy nucleation mechanism. This mechanism is apparently involved in the case of sodium citrate. According to this theory, ripening of the CG particles at a sufficient activity of the reducing agent is preceded by nucleation of the new phase and reversible aggregation–peptization of the nuclei giving structures much exceeding in size the final size of the suspended gold particles. This may be responsible for the appearance and the subsequent shift of the $\lambda = 700$ nm absorption maximum when sodium citrate is used. The activity of PEI towards the reduction of $HAuCl_4$ proved to be markedly lower. Furthermore, because of high molecular mass and adsorption on the particles (which bear a rather high negative charge), PEI had a stabilizing action on the sol. This restricted the critical size of nuclei of the new phase to a value comparable, in the order of magnitude, with the final size of CG particles, decreased the particle growth rate and prevented aggregation. This is evidenced by the position of the absorption maximum of the formed sol at $\lambda = 520$ nm being invariable with time.

In this case, the mechanism of formation of nanoparticles differs fundamentally from the classical one. In the initial stage, gold ions are adsorbed on the polymer chains and then they are reduced at the polymer functional groups (aldehyde or hydroxyl groups). No aggregation takes place, evidently, due to the stabilizing action of the polymer. This is confirmed by TEM data, according to which a part of the reduced CG formed with a deficiency of PEI exists as small particles (about 1 nm), that is, as nuclei adsorbed on polymer chains. This may result in the formation of associates of polymer chains with CG particles of both types (both ripened particles and stabilized nuclei), as shown in Fig. 6.

A change in the $HAuCl_4$: PEI molar ratio may induce programmed formation of dimers and trimers[163] and the formation of nanoparticles of different size: the ratios 3 : 1, 6 : 1 and 9 : 1 result in the formation of particles with diameters of 13, 17 and 20 nm, respectively.[164] The synthesis conducted at room temperature occurs approximately within 6 days.

For the synthesis of gold hydrosols in a one-stage process, PVP was used without addition of another reducing agent at temperatures from 25 to 70 °C.[165] The reduction lasted for 4 h. It was shown that the shape, size and optical properties of the resulting particles can be controlled by varying the PVP to $HAuCl_4$ ratio. The authors suggested that the reduction proceeds *via* partial degradation of the polymer during the nanoparticle synthesis.

Xiong *et al.*[166] prepared gold sols using PVP as the reducing and stabilizing agent at 56 °C. The authors suggested that mild reduction of $AuCl_4^-$ involves the reactive terminal hydroxy groups of the polymer formed as a result of participation of water and hydrogen peroxide in the polymer production. The authors confirmed that the PVP to $HAuCl_4$ ratio and polymer molecular mass are the factors that control the reduction rate and the shape of the desired particles.

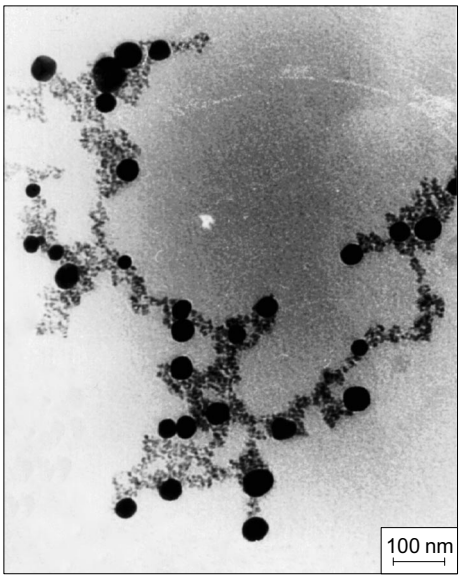


Figure 6. TEM image of colloidal gold particles obtained by reduction of $HAuCl_4$ with polyethyleneimine with a deficiency of reducing agent.[162]

A method using PVP as the only reducing agent for fast (10 min) synthesis of ultrastable gold sols at room temperature was developed.[167] The diameter of the nanoparticles thus formed was 6–17 nm. The initiation and control of the reaction rate were accomplished by introduction of a NaOH solution into the reaction mixture.

In addition to the most popular polymers such as PEG, PEI and PVP, other polymers were used more rarely for one-step CG synthesis, namely, polydithiafulvene,[168] sodium polyacrylate,[169, 170] poly(ethylene oxide)–poly(propylene oxide) block copolymer,[171] polyacrylamide,[172] polyallylamine,[173] polyphenols,[174, 175] poly(L-lysine),[176] polydimethylaminoethyl methacrylate.[177] In addition, surfactants such as acetylene glycol,[178] oleylamine,[179, 180] oxyethylenediamine[181] and Tween 80[182] and organic compounds such as disulfanylsuccinic acid[183] or cycloketones[184] were used in CG synthesis.

Thus, published data demonstrate the possibility of preparing CG using synthetic polymers as reducing agents. The gold nanoparticles obtained in this way are characterized by size and shape uniformity. Since the gold particles are formed with a protective polymer coating, sols of this type are stable on storage and are suitable for medical and biological applications, in particular, to study the nanoparticle penetration into cells and conjugation to medicinal agents and DNA (RNA) for drug delivery into organs and tissues of the body. The mechanism of formation of these nanoparticles differs from the classical one observed when low-molecular-mass compounds serve as reducing agents. Typical absorption spectra recorded during the growth of

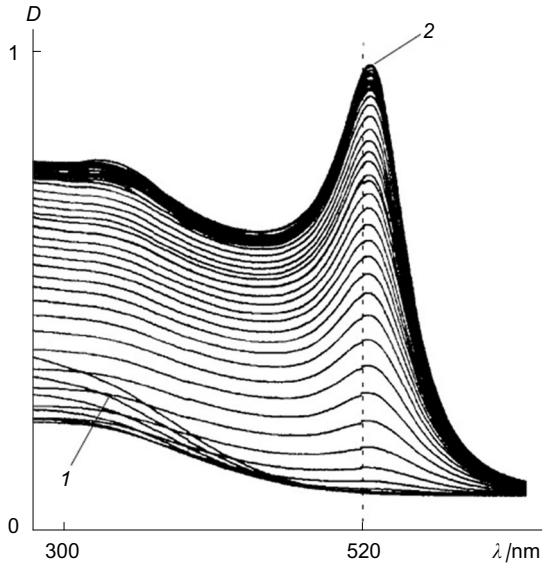


Figure 7. Time evolution of the absorption spectra of gold sols during the reduction of $HAuCl_4$ with polyethyleneimine.[162] (*1*) Decrease in the absorbance in the short-wavelength spectral region, (*2*) smooth growth of the absorbance with an absorption maximum at 520 nm.

nanoparticles in the presence of polymeric reducing agents and characterizing the process are presented in Fig. 7.[162]

7. Synthesis of gold nanoparticles using biomolecules

By analogy with the use of synthetic polymers for CG synthesis, it is possible to employ biopolymers and small biomolecules for the preparation of gold nanoparticles. Like synthetic polymers, biopolymers can be used both in combination with other reducing agents and as single reducing agents and stabilizers for nanoparticles.[185]

An example of the former approach is the preparation of CG in the presence of the aminopolysaccharide chitosan and sodium borohydride.[186, 187] The average size of gold nanoparticles varied from 6 to 16 nm and was considerably affected by the concentration of the added chitosan. The antioxidant activity of the gold – chitosan complex was 80 times as high as that of the ascorbic acid. Chitosan-coated gold nanoparticles conjugated to ampicillin showed pronounced antibacterial activity.[188]

The second approach is exemplified by the synthesis of chitosan-stabilized gold nanoparticles with chitosan being the only reducing agent.[189, 190] According to spectrophotometric data, the kinetics of nanoparticle synthesis resembled, in this case, the kinetics of chloroaurate reduction with synthetic polymers. The size and shape distributions of gold nanoparticles varied with the variation of chitosan molecular mass and concentration. Potara *et al.*[191] showed that the reaction temperature plays a crucial role in the control over size, shape and crystal structure of nanoparticles for chitosan as the reducing agent. A stronger bond between the gold nanoparticles and the polymer was attained by reduction of $HAuCl_4$ with thiolated chitosan.[192] The kinetics of CG synthesis with chitosan as the reducing agent was studied; it was shown that the reduction is accomplished by numerous amino and hydroxyl functional groups present in chitosan.[193]

The biocompatible CG – chitosan complex with attached insulin was proposed for trans-mucosal drug delivery.[194] The gold – chitosan nanocomposites have found use in biosensor devices[195] and as platforms for surface-enhanced Raman scattering (SERS).[191] A method for CG preparation was developed using chitin, the chitosan precursor, as the reducing and stabilizing agent.[196]

Stable gold nanoparticles with a diameter of 18 – 40 nm were generated using yet another aminopolysaccharide, aminodextran, as the only reducing agent.[197, 198] The diameter of the resulting particles was controlled by varying pH, temperature and Au^{3+} to aminodextran ratio. Dextran was also employed for CG preparation, besides aminodextran.[199] The doxorubicin conjugate with dextran-coated gold nanoparticles was used to deliver a cytostatic to cell nuclei.[200]

A complex natural polysaccharide, gum arabic (made of hardened sap of various species of the acacia tree), was employed as the reducing and the stabilizing agent to prepare CG.[201 – 203] The diameter of the final particles depended on the reaction temperature and reactant ratio. The nanoparticles thus formed were used, as complexes with doxorubicin, for the drug delivery to tumour cells. The reduction of $HAuCl_4$ with isoascorbic acid in the presence of gum arabic resulted in the preparation of virtually monodisperse spherical particles 80 nm to 5 m in diameter, depending on the acidity and concentration of the reducing agent.[204, 205] Arabinogalactan, a component of larch gum, is also able to reduce chloroaurates to gold nanoparticles.[206]

Other natural polysaccharides — pectins (polygalacturonates) — were shown to be applicable for one-step CG synthesis.[207] The presence of hydroxyl, ester, carboxyl and amino groups, which react with metal ions more or less efficiently at different pH, determines the reactivity of pectins towards gold reduction. The CG samples thus obtained retained high stability, their optical properties remaining invariable during a 5-year observation period. Gold – pectin nanocomplexes coated by doxorubicin and folic acid were applied for targeted drug delivery to a breast tumour.[208] The attachment of azidothymidine, an antiretroviral agent, to the complex provided the delivery into rat macrophages, which may be used to develop new drug dosage forms.[209]

Stable gold sols with a narrow particle size distribution were also prepared with simultaneous use of glucose as the reducing agent and starch as the stabilizing agent.[210, 211] The synthesized nanoparticles proved to be non-toxic towards some animal cell lines; therefore, they are promising for the use in theranostics.[212] A very fast synthesis of CG at room temperature takes place on simultaneous treatment with ascorbic acid and saccharose.[213] Monodisperse (13 nm) gold nanoparticles were prepared at room temperature by means of reduction with various glycosides in an aqueous NaOH solution.[214] It was shown that the process of reduction is affected by the chemical structure of glycons and aglycons and their ratio in the glycoside molecule. Colloidal gold synthesis using carrageenan oligosaccharides[215] and mono- and disaccharides such as fructose, glucose and saccharose[216, 217] were reported.

Apart from polysaccharides, other biopolymers such as proteins and oligopeptides are also suitable for CG preparation.[218] A one-step synthetic procedure was developed for

the preparation of a specific biomarker, a CG–immunoglobulins conjugate, by combined use of a protein and sodium borohydride for the reduction of $HAuCl_4$.[162] The resulting biomarker (CG–immunoglobulin G conjugate) was tested for specific activity by dot blot analysis. This biomarker did not differ in sensitivity from that prepared by the conventional method, that is, protein conjugation with ready gold nanoparticles. Furthermore, sodium borohydride is applicable for one-step synthesis of gold nanoparticle conjugates with haemoglobin and bovine serum albumin (BSA).[219–222] The latter was subsequently used for the conjugation to aminoglycoside antibiotics.

A simple and convenient synthesis of gold nanoparticles in a foam layer using BSA was reported.[223] Bovine serum albumin is an excellent foaming agent and, being zwitterionic at the protein isoelectric point, it can be employed for binding to gold ions in the foam. Then the metal ions are reduced *in situ* to give gold nanoparticles. The BSA molecules cover and stabilize the nanoparticles obtained in this way, thus excluding the need for another stabilizing agent.

Surfactants were also applied to prepare gold nanoparticles in the presence of denatured BSA.[224] Cationic surfactants induce protein denaturation at a lower temperature than anionic or zwitter-ionic surfactants because of stronger electrostatic interaction with BSA. The complexes thus prepared had low cytotoxicity and were recommended as carriers for targeted drug delivery and other biomedical applications. Apart from BSA, the ability to reduce chloroaurates was demonstrated for human serum albumin (HSA).[225, 226] It is noteworthy that BSA is one of the key matrices for the synthesis of luminescent gold nanoclusters with a relatively small (< 30) number of gold atoms.[227]

Interesting results were obtained by using gelatine for reduction and stabilization of gold nanoparticles. The final nanoparticles obtained in this way were found to affect osteoblast proliferation and differentiation.[228] Gold nanoparticles obtained by reduction of $HAuCl_4$ with collagen had low cytotoxicity and good biocompatbility and efficiently penetrated into cells.[229] Mehta *et al.*[230] proposed using trypsinized casein, tryptone, for CG preparation.

Some enzymes immobilized on gold nanoparticles retain or even increase their biocatalytic activity.[231] Therefore, it appears reasonable to employ them for CG synthesis. When $HAuCl_4$ was reduced with α-amylase and *Eco*RI endonuclease, the enzymes did not lose the catalytic activity.[232] Meanwhile, other enzymes such as ribonuclease A, lysozyme, alkaline phosphatase, peroxidase, *Taq* DNA polymerase and *Pvu*II endonuclease did not reduce chloroaurates to nanoparticles. The structural analysis of enzymes demonstrated that both α-amylase and *Eco*RI endonuclease have free accessible S–H groups in the native form and, hence, they are suitable for reduction, whereas the other enzymes are devoid of these groups. The α-amylase active site is located opposite to an open S–H group, which makes this enzyme an optimal agent for the synthesis of nanoparticles and binding to gold *via* the Au–S bond, with the enzyme biological activity being preserved.

The application of trypsin for the preparation of CG has been reported.[233] The presence of specific amino acids, such as cysteine, methionine and tyrosine, in the trypsin molecule in combination with unique three-dimensional structure makes this enzyme suitable for binding and reduction of $AuCl_4^-$ ions, resulting in the formation of gold nanoparticles.

Enzymes isolated from fungi, *e.g.*, oxidoreductases, phenol oxidases and pectinases, from bacteria (subtilisin, a serine endopeptidase; sulfite reductase) and from plants (bromelain protease) are also able to reduce $HAuCl_4$ to gold nanoparticles.[225, 234–238] Note that the nanoparticle growth kinetics involved in the reduction with proteins barely differs from the kinetics observed with synthetic polymers and polysaccharides.[239, 240]

A similar situation was observed when $HAuCl_4$ was reduced by peptides with different qualitative and quantitative composition of amino acid residues.[241, 242] Tyrosine and tryptophan were found to play the key role in the reduction.[243, 244] Meanwhile, the CG syntheses using single amino acids as the only reducing agents were carried out with aspartic acid;[245, 246] L-tyrosine, glycyl-L-tyrosine and L-arginine;[247] glutamic acid and sodium glutamate;[248, 249] cystine;[250] L-leucine;[251] and biotinylated ditryptophan.[252] Maruyama *et al.*[253] investigated the ability of 20 amino acids to reduce $HAuCl_4$. On treatment with some amino acids (asparagine, alanine, aspartate, glycine, histidine, leucine, lysine, serine, tyrosine and valine), solutions assumed colours typical of colloidal gold solutions. The use of arginine, cysteine, glutamine, glutamate, isoleucine, proline or threonine did not give colloidal gold. Methionine, phenylalanine and tryptophan generated unstable colloids, the particles of which rapidly precipitated.

Apart from biomolecules, other organic compounds were used to prepare CG: amino alcohols,[254] luminol,[255] glycerol,[256] nitriloacetic acid,[257] oxocarboxylic acids,[258, 259] sodium rhodizonate,[260] nicotinamide adenine dinucleotide[261] and buffer solutions containing organic compounds.[262, 263] Some gold nanoparticles obtained in this way were proposed for biomedical applications.

8. Synthesis of gold nanoparticles using therapeutic agents

Targeted drug delivery is a prominent challenge of modern medicine. Nanoparticles, including gold nanoparticles, can serve as carriers for drug delivery.[264, 265] Usually, therapeutic agents are conjugated to ready nanoparticles or gold nanocomposites.[266] However, there are methods in which drug substances are directly used as reducing agents in the CG synthesis.

Dopamine hydrochloride, a neurotrasmitter with cardiostimulatory, vasodilatory and diuretic effects, stimulating dopamine receptors was among the first drugs applied to prepare CG.[267] It is used for the treatment of shock conditions, functional renal failure, chronic myocardial insufficiency and Parkinson's disease. Using a mixture of the neurotransmitter and the nonionic surfactant Triton X-100, the authors synthesized gold nanoparticles 3 nm in diameter at room temperature. It was shown[268] that Au^{3+} ions are reduced after dopamine oxidation to quinones, which then react with dopamine to give semiquinones. After that, semiquinones serve as the initial reducing agents for Au^{3+} ions to give nanoparticles.

The flavonoid silymarin isolated from seeds and fruits of Milk thistle (*Silybum marianum* L. Gaertn) is widely applied to treat liver diseases as a hepatoprotective agent. Silymarin-coated gold nanoparticles with an average size of 20 nm were synthesized and functionalized using silymarin as a reducing and stabilizing agent.[269] The therapeutic effect of silymarin-coated gold nanoparticles was demonstrated

against liver damage and cirrhosis in laboratory animals. The conjugate-promoted degradation of the extracellular matrix and inactivation of serous cells with strong enhancement of the regenerative ability of the liver. Silymarin-coated nanoparticles can be injected during up to 14 weeks without adverse effects or changes in the histological structures of kidneys, heart, pancreas or lungs. In addition, antitumour effect was found for silymarin immobilized on gold nanoparticles.[270] Similar results were obtained using a gold nanoparticle–luteolin conjugate synthesized by direct reduction of auric chloride by this flavonoid.[271]

In order to fabricate a new dosage form of a diagnostic agent, 5-aminolevulinic acid, it was used in one-step synthesis of a conjugate with gold nanoparticles.[272] Due to specific metabolism in tumour cells, 5-aminolevulinic acid causes accumulation of photoactive porphyrins in the epithelial and tissue neoplasms and in atherosclerosis plaques. Therefore, this compound is utilized for visualization of pathological tissues. For the same reason, 5-aminolevulinic acid is used as a diagnostic and therapeutic agent in the photodynamic therapy, which not only efficiently visualizes the tumour sites due to the contrast of protoporphyrin IX red fluorescence upon short-wavelength excitation, but can also directly destroy the surface or cavernous tumours owing to its photodynamic activity. The nanoconjugate was tested in animals and proved itself as an efficient highly sensitive theranostic agent promising for early diagnosis and therapy of atherosclerosis.

One more anti-atherosclerotic agent (possessing also antitumour activity) — epigallocatechin 3-gallate — was used to reduce $HAuCl_4$ and to prepare a conjugate with gold nanoparticles.[273] The conjugate possessed low toxicity towards healthy tissues and suppressed development of stenosis in laboratory animals with cardiovascular diseases.

Folic acid (vitamin B_9) is often applied for targeted delivery of anticancer agents as a targeting molecule recognizing tumour cells. This is due to the fact that cancer cells overexpress folate receptors on the surface. It was found that folic acid is suitable for one-step synthesis of gold nanoparticles in alkaline medium.[274] The obtained gold nanoparticles (18 nm) penetrated into HeLa cells much more efficiently than the non-conjugated particles of the same size, with this penetration being considerably inhibited by free folic acid in competitive analysis.

The antitumour agent, 3-hydroxymethylindole, can reduce chloroaurates to give metal nanoparticles, while acting as both the reducing and stabilizing agent.[275] The stable conjugate thus formed (particle diameter 3 nm) showed pronounced cytotoxic, genotoxic and antitumour effects *in vitro* by inducing apoptosis of tumour cells.

Sharp increase in the prevalence of bacteria with multiple drug resistance all over the world causes high demand for the development of new-generation antibiotics to fight these bacteria. One of the ways to enhance the action of antibiotics is their incorporation into targeted delivery systems, in particular, *via* conjugation to nanoparticles. For this purpose, some antibiotics were used for direct synthesis of conjugates with gold nanoparticles. Indeed, cefaclor, a cephalosporin antibiotic, was employed to prepare 20–50-nm nanoparticles.[276] The diameter of the obtained particles depended mainly on the reaction temperature. The reduction was accomplished by the primary amino group of the agent, while the β-lactam ring of cefaclor remained free for the antimicrobial action. Microbiological assays showed that cefaclor conjugated with gold nanoparticles possessed higher antimicrobial activity against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria than non-conjugated cefaclor or gold nanoparticles. The conjugate proved to be highly stable under unfavourable conditions (pH 3 and 10) and was repeatedly usable with retention of the activity.

The antibiotics ampicillin, streptomycin and kanamycin were employed for $HAuCl_4$ reduction, together with sodium borohydride. The resulting conjugates exhibited higher

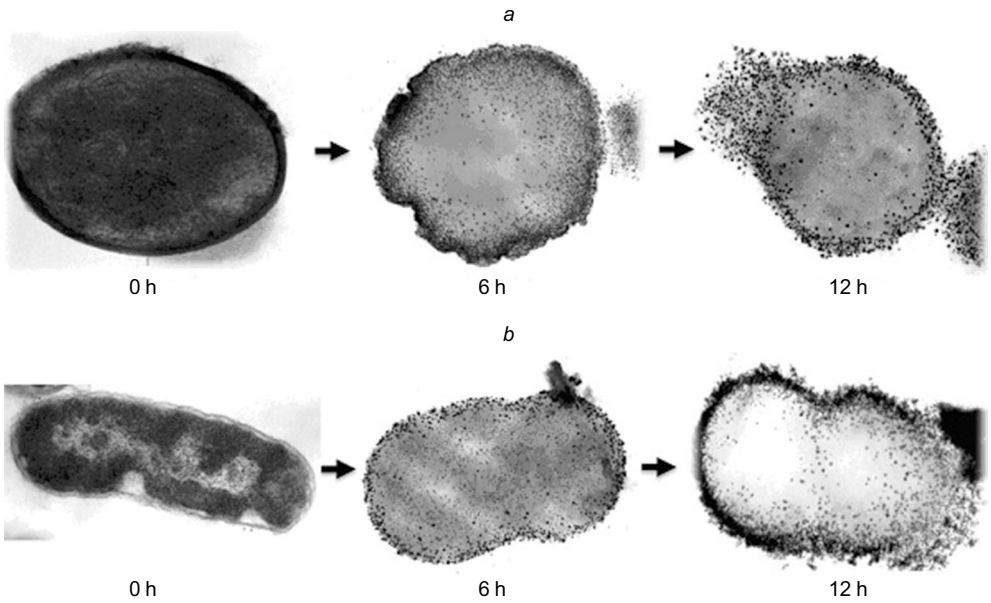


Figure 8. TEM images of the morphological changes in bacterial cells under the action of the kanamycin–CG conjugate.[278] (*a*) Gram-positive bacteria *S. epidermidis*, (*b*) gram-negative bacteria *Enterobacter aerogenes*.

antibacterial activity than the non-conjugated antibiotics.[277]

Kanamycin, an aminoglycoside antibiotic, was used in a one-step synthesis of the conjugate with gold nanoparticles.[278] Bacteriological tests showed dose-dependent activity of the conjugate with a broad range of action against both gram-positive and gram-negative bacteria, including kanamycin-resistant ones (Fig. 8). It was shown that after 6 h of treatment, the kanamycin–CG conjugate is attached to the bacterial cell wall and penetrates inside, thus disrupting the intracellular homeostasis. After 12 h of treatment, cell lysis takes place due to leakage of cell components. Also, the minimal inhibitory concentration of the kanamycin conjugate with 20-nm gold nanoparticles was markedly lower than that for free kanamycin for all of the tested bacterial strains.

A semisynthetic penicillin type antibiotic, amoxicillin, was also used for one-stage preparation of the conjugate with gold nanoparticles.[279] Amoxicillin-coated nanoparticles possessed high *in vivo* stability and selectivity to the bacterial cell wall; they were efficiently excreted by kidneys and were completely non-toxic for eukaryotic cells at bactericidal concentrations. The resulting conjugates possessed a strong antibacterial action *in vitro* against antibiotic-sensitive and -resistant *S. aureus* bacteria. In view of their stability and cytocompatibility, these nanoparticles are promising for treatment of antibiotic-resistant infections.

9. Conclusion

The history of preparation of colloidal gold dates back to Chinese, Arabian and Indian treatises of the 5th–6th centuries BC, works of medieval alchemics and classical studies of Faraday, Zsigmondy, Svedberg and Mie. The contemporary history of colloidal gold coincided with the beginning of the 21st century and development of nanotechnologies, which actively utilize the unique optical, catalytic and electrochemical properties of gold nanoparticles. As a result of nearly 25-year studies, methods for chemical synthesis of CG particles of various size, shape and structure were developed.[280,281] However, roughly spherical nanoparticles remain in demand in many fields of fundamental science and practice. In this review, we discussed numerous protocols of the citrate synthesis of GC, which was first described in 1934 by Russian researcher D.P.Borowskaja [59] (the citrate method is known from the literature as the Turkevich method, Frens method or Turkevich–Frens method).

According to classical Zsigmondy's view, the mechanism of growth of CG nanoparticles includes the formation of nuclei *via* nucleation of reduced gold atoms and the stage of particle growth as a result of nuclei coagulation. Although previously it was considered that this classical scheme proposed for reduction with hydrogen peroxide is largely valid for the citrate synthesis, neverthess, citrate synthesis has its own specific features. In particular, in the citrate synthesis, the particle size is determined by the balance between the rates of nucleation and degradation of dicarboxyacetone formed in the reaction rather than by the balance between the nucleation and growth rates. It is possible that both balances affect, to different extents, the CG particle size in the citrate synthesis, especially at high concentrations of the citrate where the role of nuclei coagulation is high.

According to the modern views, a key role in the citrate synthesis of CG is played by the solution pH, which was ignored in earlier studies of the growth mechanisms.[282] In particular, at pH >6.2, the reaction is controlled by the $[AuCl_2(OH)_2]^-$ and $[AuCl(OH)_3]^-$ ions with low reactivity, which results in the formation of sols with a narrow size distribution. For pH $\leqslant 5-6.2$, the particle formation is controlled by highly reactive $[AuCl_3(OH)]^-$ ions, which leads to sols of irregularly shaped particles with a broad size distribution. Usually pH of the reaction mixture is specified by the $HAuCl_4$ to citrate ratio, which gives rise to an undesirable correlation between the particle size and shape: as the size increases, the shape becomes more irregular and more non-spherical. However, regulation of the pH (*e.g.*, by adding a NaOH solution at certain time points during the reaction) makes it possible to control the growth and, in particular, to obtain particles with 6–15 nm size, *i.e.*, this decreases the size limit of the citrate synthesis. It should be noted that the data on the pH effect on the mechanism of citrate synthesis were confirmed by molecular and mathematical modelling and NMR spectroscopy.

The whole set of available data on the citrate synthesis indicates that the key control parameters of the reaction are the ratio of $HAuCl_4$ to sodium citrate concentrations, pH of the reaction mixture, reaction temperature and time, the order of reactant addition and the diffusion mass transfer.[90,283]

Since the lower limit of particle size in the citrate synthesis is approximately 10 nm, quite a few studies were directed towards decreasing this limit by 2–3 nm. The developed methods imply the use of sodium or potassium thiocyanate or sodium borohydride, in particular, in combination with other chemicals as reducing agents.

The two-phase Brust–Schiffrin process is the most popular approach to the preparation of gold nanoparticles in nonaqueous media. This process can serve to prepare ultradisperse aggregation-stable sols with a particle size of 1–3 nm.[284]

In order to exclude the particle stabilization stage involving various ligands, sols are synthesized in some cases using reaction mixtures containing a stabilizing agent or its precursor. The stabilizing agents are represented by various types of polymers such as PVP, PEG, PEI, *etc*. It should be noted that the indicated polymer additives can act simultaneously as reducing and stabilizing agents. The list of polymers suitable for this synthesis includes about 20 items.

The synthesis of gold nanoparticles using natural biopolymers is an actively developing trend of the colloid chemistry of gold called green chemistry. This approach solves simultaneously two issues: (1) no harsh compounds contaminating the environment are used; (2) at the end of synthesis, the final particles are often already functionalized by the desired natural compounds performing important physiological or technological functions. Furthermore, the obtained functionalized nanoparticles are biocompatible and suitable for further functionalization by the target compounds. Reducing agents of this type include chitosan, aminodextran, gum arabic, curdlan, pectins, starch, some proteins (*e.g.*, BSA), oligopeptides and so on.[285] An important advantage of green chemistry is the absence of cytotoxicity of nanoparticles *in vitro* or toxicity at the level of the whole body.

The important problem of drug delivery to biotargets using CG conjugates is solved by using synthetic protocols in which the drug is used as both the reducing agent and the surface ligand. Examples are dopamine hydrochloride, the flavonoids silymarin and luteolin and 5-aminolevulinic acid. A popular ligand for targeted delivery to cancer cells is CG-conjugated folic acid.

The use of antibiotics as reducing agents gives conjugates with enhanced antimicrobial activity. This approach is potentially suitable for solving the important problem of drug resistance of pathogenic bacteria where gold nanoparticles are also used as platforms for delivery of photodynamic agents.

Thus, this review demonstrates the great potential of mere gold nanoparticles, which have been known from ancient times, but acquired a new scientific and applied value in the age of nanotechnology. The results of published studies lead to the optimistic conclusion that spherical gold nanoparticles have not only interesting applications in modern nano- and bionanotechnology, but also great prospects.

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