



## Review

## Lanthanide-coated gold nanoparticles for biomedical applications



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## ARTICLE INFO

## Article history:

Received 21 December 2013

Received in revised form 12 March 2014

Accepted 17 March 2014

Available online 25 March 2014

## Keywords:

Lanthanide complexes

Luminescence

Nanoparticles

## ABSTRACT

The use of gold nanoparticles as a scaffold on which to assemble molecular architectures presents a versatile approach to produce nanoprobcs with modalities defined by the properties of the capping architectures at the molecular level. Lanthanide ions, with their characteristic magnetic and luminescent properties, are ideal probes for imaging applications. Gold nanoparticles represent an inert, biocompatible and rigid scaffold on which to assemble molecular complexes using clean, facile chemistries. The size of the gold nanoparticles can be easily tuned using robust and established chemistry. The combination of the stable, long-lived luminescence signal or characteristic magnetic properties afforded by the trivalent lanthanide ions with the size-tuneable inert gold core allows the formation of tailored nanoprobcs ideally suited to the investigation of biological systems and biomedical applications. In this review the different methods for attachment of lanthanide complexes onto gold nanoparticles are presented for the production of nanoprobcs with luminescence and magnetic resonance signal outputs. A short introduction outlining the development of the preparation methods for water-soluble gold nanoparticles is presented, followed by the approaches to the functionalisation of gold nanoparticles with metal-complexes which set the scene for the lanthanide studies. Two approaches of introducing lanthanides onto gold nanoparticles are identified and the systems are grouped in the discussion under the attachment of pre-assembled lanthanide complexes and the employment of ligands on nanoparticles that bind lanthanides. The preparation and properties of lanthanide-coated nanoparticles are then discussed in detail as luminescent visible and near infrared probes. Finally, the development of gold nanoparticles as a platform on which to assemble Gd(III) complexes for magnetic resonance imaging applications is discussed.

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## 1. Developments in the preparation of gold nanoparticles

The key to the popularity of nanoscale materials, and nanoparticles in particular, lies in their ease of synthesis. Colloidal synthesis provides an elegant means to access thermodynamically stable edifices that can be used as scaffolds to encode new properties whereas traditional wet covalent chemistries such as those

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used to access dendrimers, for example, are laborious for building nanoscale structures. Since the 1990s there has been huge growth in nanoparticle research. To put this in perspective, a database search in autumn 2013 by the authors using Thomson Reuters' Web of Knowledge using the topic search string 'gold nanoparticles' revealed approximately 110,000 articles and patents, while a similar search in 2007 by Wilton-Ely revealed this number to be around 2750 [1].

It is widely established from their ubiquitous use in nanoscience [2] that gold nanoparticles are the paragon for noble metal nanoparticles in this field. The production of gold nanoparticles is evident in many historical art pieces (e.g., the oft-cited *Lycurgus Cup* in which lighting affects the appearance of the colour, the latter based on the known surface plasmon resonance (SPR) of the gold nanoparticles [3]), as well as famous examples of colloidal gold from Faraday [4]. The modern field of colloidal nanoparticle synthesis was rather then not discovered but collated and quantified by Turkevich and co-workers [5], who described various reducing agents for producing gold colloids from gold salts and characterisation of the products by electron microscopy. There were two major discoveries at this historical juncture, *firstly* that reduction of the gold salt using trisodium citrate was *highly reproducible* and gave relatively tight particle size distributions in the  $d \sim 10$ –100 nm size regime compared to the other reductive methods employed and *secondly*, that the diameter of the spherical particles produced by the sodium citrate synthesis could be controlled by the gold-to-citrate ratio; this effect was later investigated and quantified by Frens, where definite size control of the gold cores in the range 10–150 nm was reported [6]. It is worth noting that these preparations are mainly carried out in aqueous solution and are therefore poised well for the modification of the nanoparticles to afford products that are compatible with biological systems.

The modification of gold surfaces by surface assembled monolayers (SAMs) comprised of  $\omega$ -alkanethiols by Whitesides and co-workers [7] brought breakthroughs in gold surface chemistry, thus forming the basis of modern nanotechnology. Leading on from this, alkanethiol gold interactions were used in the *in situ* synthesis and stabilisation of 1–3 nm diameter gold nanoparticles in organic media by Brust, Schiffrin and co-workers in a seminal work [8], the products of which were later termed 'monolayer protected clusters' or simply MPCs [9]. Furthermore, modification of the nanoparticles can be achieved either by ligand exchange methods [10] or *via* direct chemical reactions of the capping ligands [11].

The synthetic accessibility of gold nanoparticles, their size tunability and robustness under a range of chemical conditions, are all attractive properties for their employment as scaffolds on which to assemble luminescent and paramagnetic metal complexes. The resulting luminescent nanoprobes bear the characteristic properties of the metal complexes and therefore do not experience either the 'blinking' associated with semiconductor quantum dots nor unpredictable magnetic properties associated with bulk material preparation. For biomedical applications these properties provide distinct spectroscopic signatures in the nanoscale that allow tailoring of the detection methods in imaging to improve signal and prevent artefacts.

## 2. Metal complexes as biological imaging agents

Trivalent lanthanide ( $\text{Ln}^{3+}$ ) or transition metal ion (TM) lumophores offer the advantage of high photostability compared to organic dyes. Due to the fact that metal-centred luminescence, unlike organic fluorescence, commonly proceeds through higher multiplicity electronic states, the Stokes shift is usually large, >100 nm, (compare organic: typically 30 nm) and as the luminescence often arises from formally forbidden electronic

transitions which become allowed due to vibronic coupling, the lifetimes of metal complexes are usually long as the rate of radiative decay ( $k_{\text{rad}}$ ) from the luminescent state is slow. When combined with rational ligand design to minimise the rate of the non-radiative decay pathways ( $\Sigma k_{\text{non-rad}}$ ) from the luminescent state, lifetimes can extend well into millisecond timescale. The large Stokes shifts and long lifetimes observed for metal complexes have two important consequences. The first is that the excitation wavelength can be separated cleanly from the emission wavelength, and so gives good signal to noise ratio for all measurements, thus increasing sensitivity. This is especially important for biological imaging and microscopies where the separation of spectral regions is of utmost importance. If the metal complex has an excitation wavelength greater than 400 nm, signal pollution from autofluorescence from nucleic acids and proteins in such analyses is reduced. The second important consequence stems from the long lifetimes; collection of spectra using time-gated measurements effectively eliminates emission from organic fluorophores and the long lifetime acts as a signature for the detection of the complex in biological samples. In the case of the lanthanide ions, direct excitation of the ion itself has a low efficiency ( $\epsilon \sim 1$ – $10 \text{ M}^{-1} \text{ cm}^{-1}$ ) due to the forbidden nature of the  $f$ – $f$  transitions (primarily by the Laporte selection rule but some are also spin-forbidden). In this case, the effect has been circumvented by the use of organic antenna ligands which present much greater absorption cross-sections as well as being able to transfer the absorbed energy from light, usually *via* a triplet state, to the lanthanide ion, thus populating the luminescent state indirectly. The latter phenomenon is known as the absorption-energy transfer-emission (AETE) effect, or simply the antenna effect, and organic aromatic moieties which can perform this task are called sensitizers. The reviews by Coogan et al. [12] on transition metal complexes and Buenzli et al. [13,14] on lanthanide complexes clearly demonstrate the usefulness of both types of metal lumophore in biological analysis.

The use of the highly paramagnetic Gd(III) complexes as  $T_1$  contrast agents for magnetic resonance imaging (MRI) [15] has become ubiquitous in the clinic. Due to the similarity of the coordination preferences across the lanthanide series, it is extremely easy to produce ligands that can form complexes for use in both luminescence imaging and MRI.

## 3. Approaches to coating nanoparticles with metal complexes

In order to incorporate the benefits of lanthanide lumophores into nanoscale probes there have been a number of ingenious approaches by various research groups to afford nanoparticles coated with luminescent metal complexes. The first general approach relies on the *pre-assembly* of the metal complex prior to nanoparticle synthesis. In general, the ligands used to complex the metals for this application are bifunctional in nature, with sites to complex the luminescent metal centre – usually macrocyclic (e.g., DOTA) or chelating podand (e.g., DTPA) ligands consisting of a hard donor atoms such as oxygen and nitrogen that can bind the metal centre to give kinetically non-labile and thermodynamically stable luminescent complexes – and soft thiol moieties to anchor the complex onto the gold surface, taking advantage of the gold–sulfur interaction to give thermodynamically stable nanoparticles. The lanthanide complexes can either be assembled onto the nanoparticles during the reduction of the gold salt *i.e.*, as a capping ligand *in situ* or can be bound to the surface post nanoparticle synthesis *via* ligand exchange reactions. The latter approach relies on the incoming ligand binding more strongly to gold than the incumbent at the surface. Often multiple gold-binding sites are engineered into the complexes so that the interaction between the complex and the

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