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Exploring New Synthetic Strategies for the Production of Advanced Complex Inorganic Nanocrystals

Abstract: The design of new protocols for the colloidal synthesis of complex nanocrystals (NCs) with advanced functionalities, comprising both hybrid and hollow structures, and the study of their fundamental properties is of paramount importance for the development of a new generation of nanostructured materials. The possibility of tailoring the dimensional regime of NCs, along with its composition and structure, represents a landmark achievement in the control of their unique physico-chemical properties. These properties, alongside with the ability to cheaply produce high quality NCs in fairly large amounts by wet-chemistry techniques, leads to their potential applicability from materials science to nanomedicine. Within this context, this review is focused on describing a successful framework for designing synthetic strategies for the production of advanced complex NCs, integrating the development of new synthetic methods with its structural characterization, monitoring of their properties, and study of its reactivity. As a result, it is expected to provide new routes to produce robust and easy-to-process NCs in a wide range of sizes, shapes and configurations that can be explored to achieve the combination of all degrees of control, aiming to produce a complete and diverse library of material combinations that will expand its applicability in a wide diversity of fields.

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1 Introduction

The development of functional colloidal inorganic nanocrystals (NCs) has increased exponentially over the past decades offering a "toolbox" ready to be used in a wide range of applications such as materials science, catalysis, biology and medicine [1–4]. This applicability relies on their unique size, morphology and structure which determines not only their intrinsic properties but also its reactivity. This is due to the fact that, at the nanometer scale, the confinement of electrons, phonons and photons leads to a new generation of materials which have improved or new physico-chemical properties in comparison with bulk materials. The recently unprecedented size control has allowed the study of the fundamental properties of NCs, such as the size-dependent fluorescence of semiconductor NCs [5], absorption and scattering in noble metal NCs (e. g. Au or Ag) [6] and the superparamagnetic moment in magnetic NCs (e. g. Fe_3O_4 or Co) [7]. Traditionally, size and shape control has been achieved by using surface active agents (surfactants), following surfactant-mediated seeded-growth strategies [8] or by making use of the fact that different crystalline facets may grow at different ratios [9]. Besides spherical morphologies, NCs in the shape of rods, disks, cubes, prisms and branched structures have been prepared (Figure 1) [10–12]. This ability of tailoring the dimensional regime of NCs represents a landmark achievement since both size and shape dictate the peculiar physico-chemical properties of the material. These properties, alongside with the ability to cheaply produce NCs in fairly large amounts by wet-chemistry techniques, leads to their potential applicability in diverse fields, such as photonics, information storage, electronic and optical detection, medical diagnostic and treatments, photovoltaic catalysis and solar energy harvesting [13–16]. To move forward, more complex strategies and more evolved generation after generation of NCs is the natural way to go.
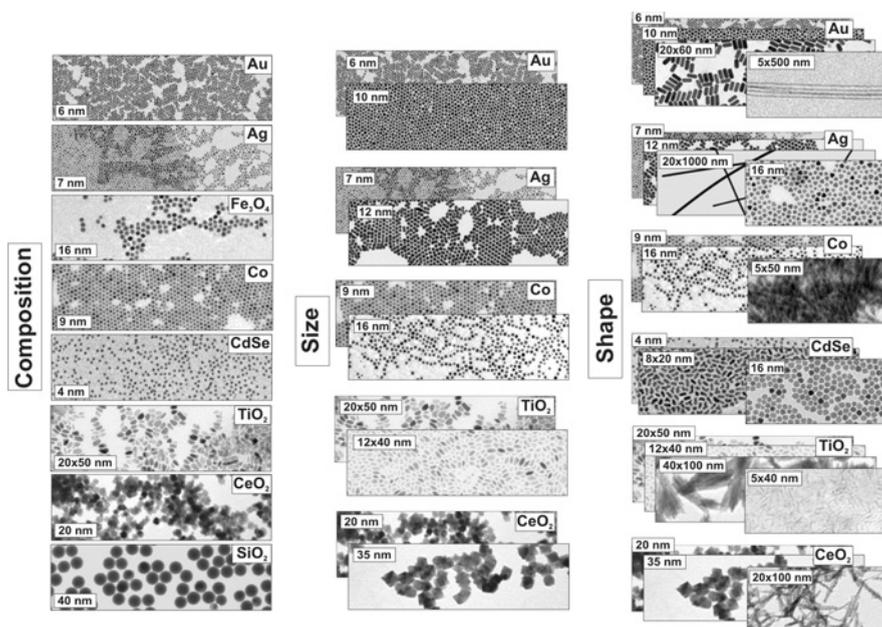
Figure 1: Control of the Composition, Size, and Shape of Colloidal Inorganic Nanocrystals. Representative Transmission Electron Microscopy images of colloidal solutions of NCs of different compositions, sizes and shapes. The control of NC's composition is achieved by the choice of the precursor. The size uniformity is achieved through the interplay of van der Waal forces and surface tension, which can be externally controlled by the concentration of the precursors, the temperature of the solution, the ligands and the solvent used. By performing NC synthesis in templates or by making use of the fact that different crystalline facets of NCs may grow at different ratios different NC's shapes can be also achieved. Labels indicate the mean NP's size for each individual composition, size and shape. For anisotropic shapes, the size of the shortest (or shortest and longest) length is provided.

2 Advanced complex nanostructures

Since the applicability of NCs is determined by their unique properties, which in turn is dictated by NC's composition and structure, the development of new synthetic strategies leading to a finer morphological control of NC's features is needed. Thus, for the same combination of materials, the properties of the resulting NCs depend not only on the material's properties of both components but also on the morphology of the particle (how each material is grown with regard to the other) and how the domains are joined together (the interface, whether there is a bond between the materials or they are brought together in close proximity us-

ing chemical linkers or by self-assembly). Additionally, beyond the control of NC's morphology, one of the most pressing questions is to understand how synthetic conditions can be controlled to join several materials that may have very different structural and physical properties (for instance alloys of immiscible materials) in a designed manner, or control the spatial configuration of multi-hollowed NCs, and do so while controlling the final NC's geometry. In this regard, as more strategies for synthesizing NCs are developed, a coherent picture how reaction conditions and materials combinations can be tuned to influence the growth mechanism of NCs is yet to emerge. Thus, it is clear that the morphological anisotropy leads to an anisotropic reactivity in the NC that allows building of hierarchical aggregations of NCs (as the deposition of a second material in the facets or the tips of a first one).

Within this context, a successful framework for designing advanced complex NCs should integrate the development of new synthetic methods with its structural characterization, monitoring of their properties and study of its reactivity, including the physico-chemical phenomena at the interface (instability of the domains, diffusion of material) and the post-synthetic modifications that take place upon interactions with the surrounding environment (dissolution, corrosion) with the aim to determine how the chemical reactivity of the NCs affects its morphology and therefore the final NC's applicability. As a result of this combined study it is expected to produce robust and easy-to-process NCs in a wide range of sizes, shapes and configurations that can be explored to achieve the combination of all degrees of control (material, size, shape and composition) in the synthesis of a new generation of advanced NCs [17]. The new synthetic mechanisms to be explored include the kinetic control of the synthesis, the use of chemical transformations at the nanoscale, the use of pre-synthesized NCs as reagents, the competitive reduction/oxidation of the precursors and the surfactant-assisted synthesis. It is important to note that diffusion solid state processes are dramatically enhanced at the nanoscale (up to 6 or 8 orders of magnitude). This allows now to consider the NCs as reagents, which efficiently compete with the chemical processes occurring in the liquid phase surrounding the NCs, rather than finished products. While macroscopically chemical reactions occurring in the bulk phase are normally restricted to study aging of materials and corrosion processes, at the nanoscale, diffusion and migration of atoms inside the solid matrix allows to produce exotic materials by unexpected ways, as in the case of the transformation of NC's composition maintaining its morphological integrity [18] and the carving of complex patterns in multi-metallic hollow NCs [19]. Similarly, the NCs can be used as a source of both ions and electrons to reduce cations and use them, for instance, as sacrificial templates [20]. All this increased reactivity, together with the catalytic and substrate characteristics of NCs, opens a new dimension for the

synthesis of an advanced generation of complex nanostructures where NCs are used as reagents to build more complex ones, sequentially and endlessly. This will allow designing applications based on responsive NCs which previously was observed but not yet controlled. This is the case of the dramatic decrease of the melting temperature when the material was reduced at the nanoscale [21] due to the modification of surface energies, diffusion coefficients and tolerance to crystal strain and defects [22] and their easiness for annealing [23]. In the same direction, the reversible conformational modification of the atomic distribution in Rh-Pd and Pt-Pd core-shell NCs depending on the NC's chemical environment was also previously observed [24]. In parallel, it is also important to note that the recent development on NC's synthesis has been enabled by a previous significant progress on the understanding of the processes involved in the balance of mass distributions at the nanoscale. Recent advances in atomic-scale characterization techniques as aberration-corrected electron microscopy and the high resolution of synchrotron sources, coupled to the development of predictive atomic scale modeling and simulations, has allowed the design and development of new synthetic strategies which yield a new and advanced (next generation) of NCs.

3 Hybrid nanostructures

The wide applicability of inorganic NCs can be increased by designing NCs with a finer morphological control of their composition and structure. A tremendous effort has been directed in the recent years towards the design and synthesis of multicomponent NCs which combine two or more component materials into one individual structure, which exhibit unique characteristics that are not just the addition of the properties of the constituent materials [25–34]. Such complex structures have the potential to combine magnetic, plasmonic, semiconducting and other physical or chemical properties into a single object, therefore providing an increased functionality (Figure 2). First efforts began with core-shell hybrid NCs (HYNCs), whereby the NC's core and the shell are composed of different materials such as combinations of semiconductors [35], in which the outer shell of a higher band gap material increases the robustness and enhances the photoluminescence (PL) quantum yield of the core, as well as magneto-plasmonic NCs [36, 37], and culminated in morphologies that deviate significantly from core–shell architectures. Among them, i) heterodimers made of spherical domains [29, 33, 38–44], ii) dumbbell-like HYNCs based on the selective growth of domains on one or both tips of a nanorods (NRs) [31, 32, 34, 45–48], and iii) other structures such as branched or pyramidal-shaped NCs decorated with several domains [45, 49, 50]. In all of
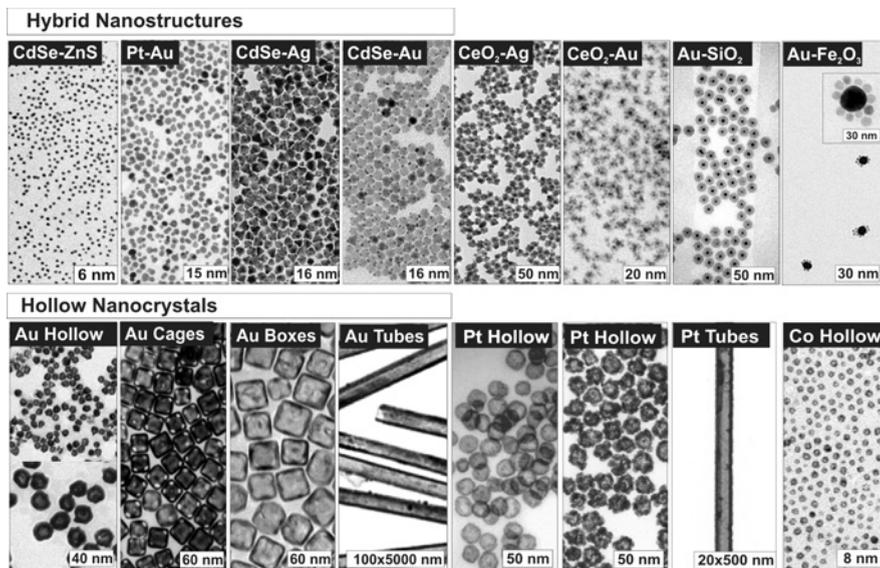
Figure 2: Advanced Complex Inorganic Nanocrystals: Hybrid Nanostructures and Hollow Nanocrystals. Representative images of Transmission Electron Microscopy of colloidal solutions of hybrid nanostructures and hollow NCs of different compositions and morphologies showing a fine morphological control of their composition and structure. Labels indicate the mean NC's size. For hollow structures, the size of the outer shell is provided.

these cases, the increased and often new functionality coming from the synergetic combination of parent properties allows to expand the already wide applicability of NCs [28, 51, 52]. HYNCs in which spherical, rod or branched sections are connected in a controlled morphology present promises for a number of potential uses ranging from nanoelectronics to biomedical, photovoltaic and catalytic applications [52–54]. Thus, magnet-semiconductor NCs are very interesting as dual-use biological tags offering the ability to visualize labeled cells using both magnetic resonance and fluorescence imaging techniques while external magnetic field may be employed for the directed assembly of such materials. Core-shell magneto-plasmonic HYNCs have been proposed as bi-functional systems for a variety of applications in theranostics, in which the metal shell acts as a protecting agent for the magnetic core, as a highly functionalizable surface [55]. Similarly, metal-semiconductor heterodimers are ideal candidates for solar energy harvesting applications, and in particular photocatalysis, in which light is converted into chemical energy. Thus, the semiconductor part of the HYNCs can be tailored for optimal light absorption while the combination with the metal part

facilitates charge separation and the reactive metal surface with a large surface area can serve as the proper catalytic substrate for the reactions [49, 56].

In addition to the growth of crystal domains onto seed NCs, the self-assembly of different materials into a single nanostructure represents another powerful strategy for the production of complex NCs. These self-assembled HYNCs composed by two or more discrete materials linked together by organic molecules are considered as a new class of multifunctional materials with interesting applications [57–59]. Despite its versatility in terms of tunability of its composition, spatial arrangement of the NCs within the structure and control of its morphology, the yield of products is still low, and consequently, a general method for the preparation of functional hybrid superstructures with tailored properties by this strategy is difficult to achieve [60, 61]. To precisely tune the composition and spatial configuration of these HYNCs, different strategies have been explored usually based on tailoring NC's ligand shell to control the posterior self-assembly of individual component. The simplest approach is the use of Van der Waals forces and electrostatic interactions [62–65], hydrophobic and hydrophilic [66, 67], or cationic and anionic [68]. Besides, the precise recognition and selectivity of biological molecules have been employed for further multicomponent NC's building. First studies, pioneered by Seeman [69] and followed by Alivisatos and Mirkin, reported the organization of NCs derivatized with single-stranded DNAs in periodic arrays and oligomeric assemblies of Au [70–72] or CdSe NCs [73]. These studies were extended to the formation of multi-component structures composed by a central QD and a discrete number of Au NCs (one to seven) attached to it [74]. Similarly, the direct assembly of NCs, often monocomponent, was achieved by using antibodies, peptides [75, 76], and organic molecules [77, 78] which led to well-defined arrays of dimers, trimers, tetramers and other superstructures of NCs. More recently, the complexity of these structures was extended to the control of its composition, showing the possibility to combine metal and semiconductor NCs into oligomeric structures either through chemical reactions of active groups present in organic molecules at their surface [79, 80] or using proteins as a templates [81].

4 Hollow nanocrystals

A finer morphological control can be also achieved by synthesizing NCs with hollow interiors (Figure 2). These hollow NCs (HONCs) exhibit surface plasmonic properties and catalytic activities that are different from (and in some cases, superior to) the solid counterparts. The unique structure of HONCs, the presence of two surfaces (internal and external) and the existence of both cavities and

pores in the wall surfaces are responsible for their unique applications [19, 82]. HONCs are potentially useful in many types of applications including their use as ultrahigh fillers to produce electrically and thermally conductive composites, plasmonic devices and catalysts [83]. Among all, nanostructures with hollow interiors have been extensively studied for their applications in microencapsulation (a process useful in many areas including catalysis, drug delivery and environmental protection). When used as fillers in preparing composites, HONCs present some advantages over their solid counterparts in terms of lighter weight, saving of material and reduction of cost. Additionally, HONCs exhibit superior surface plasmonic properties and catalytic activities. For instance, Au nanoshells can present a strong absorption in the NIR region (even stronger than other solid geometries such as rods) which enables them to be used as photothermal triggers for drug delivering and as contrast-enhancing agents in optical imaging [84].

For the study and harnessing of NC's surface properties, the interior of the NC is of little use. In relevant phenomena such as catalysis, Surface Enhanced Raman Spectroscopy (SERS), or when studying designed surface functionalization properties, there is no need of the inner NC's core. One can save it, which, even considering the high surface-to-volume ratio at the nanoscale, it only represents 50% of the total NC's mass (for a c. a. 20 nm NC, assuming 2 nm of shell thickness). This is significant, mainly in expensive noble metals such as Pt, or when NCs are administered to patients, since the use of hollow NCs reduces the cost and dose, respectively. Optical properties of metal NCs, as surface plasmon resonances, originate at the surface and are boosted in the presence of nanometric cavities. Additionally, as hollow NCs are lighter, they may have apparent densities similar to those of the proteins, and if conveyed with size, surface charge, and hydrophilicity, these NCs may travel inside the body just as much as a protein would do, being highly biocompatible. Needless to say is that there are plenty of pathways inside the body for the optimized distribution of proteins. At the end, one has also to balance the added step of sacrificing a template with the reduction of the material used, considering the intrinsic NC's physical and chemical properties of both types of structures. It is worth noting here that while the appealing optical properties of noble metal NCs at the nanoscale is a surface phenomenon, this is not the case of magnetic NCs, where the whole NC is contributing, and thus, no appealing magnetic properties have been yet observed in hollow magnetic NCs where the excess of surface and the inter-grain boundaries dump and harden the magnetic response.

There are different pathways to produce hollow NCs, principally *via* galvanic exchange and Kirkendall effect. The first method carves voids from the outside towards the NC's core while the second produces voids when the element close to the surface migrates towards the exterior of the NC leaving a vacancy behind.

Then, as the number of vacancies increases, they coalesce forming voids. Finally it is important to point out how it is really surprising that the template geometry is so well preserved during the corrosion process since in principle one would expect that the more reactive sites should corrode faster, therefore expecting smoothed corners and edges, or even at defects. Independently of the synthetic route used for its production, the design and development of synthetic protocols to combine and arrange materials that may have very different structural and physical features (for instance alloys of immiscible materials and materials with a very different lattice mismatch) and/or produce NCs with hollow cavities with controlled morphology and spatial arrangement is one of the most challenging chemical problems nowadays.

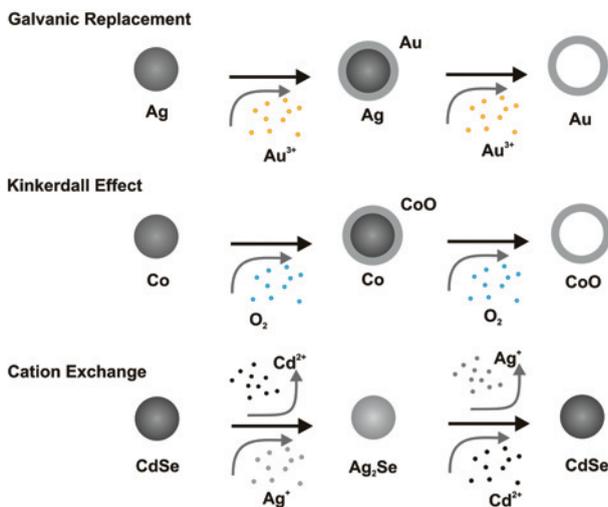# 5 Synthetic strategies for the production of advanced complex nanocrystals

5.1 Kinetic control

Since the beginning of the new age of NC's synthesis in the late 1990s, the impact of the kinetics and their out-of-equilibrium state has been acknowledged as fundamental aspect of its nature [85]. This implies both, high difficulty in reproducibility and extreme versatility in morphology, which is translated into the fact that minute modifications of the original recipes leads to very different NC's morphologies and therefore properties [86, 87]. Since then, the kinetic control of the synthesis of NCs has been evolving and developing, leading to more and more complex and artificial nanostructures. The kinetic control of NC's morphology has been proved effective to control nucleation and growth [23]. The controlled dosing of reagents (rather than the exact amounts of reagents employed) can kinetically trap NCs into metastable states or modify the formation of the sub-products of the reaction in such a way that the final result depends not only on the amount of reagents used but also on the way the reagents are added [88, 89]. Thus, starting from the same amount of precursor one can obtain a large amount of small particles or a fewer larger ones. This kinetic control involves the way of dosing the reagents, the critical temperatures for nucleation, the diffusion and growth processes, and the use of organic molecules to manipulate the states of the precursor to NC's intermediates (Figure 3). Thus, for example, one can use poorly soluble precursors to keep reagent concentration in solution constant during the reaction or lower the temperature to refocus the size distribution of the NCs while preventing the nucleation of new NCs and delaying the "defocusing" (Ostwald ripening)
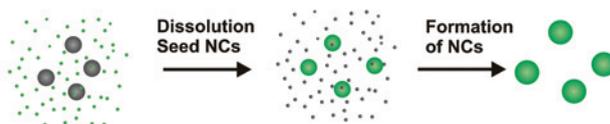
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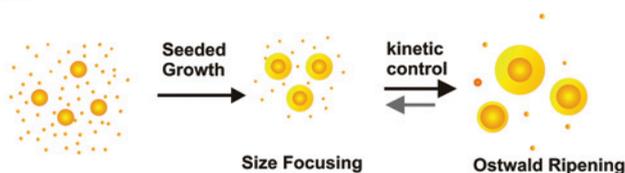
Chemical Transformations

Use of Nanocrystals as Pure Reagents

Figure 3: Synthetic Mechanisms for the Production of Advanced Complex Inorganic Nanocrystals. The new mechanisms include the kinetic control of the synthesis, the use of chemical transformations at the nanoscale and the use of pre-synthesized NC as reagents among others.

period [90]. A model example of kinetic control can be found in the recently reported strategies for the synthesis of monodisperse citrate-coated spherical Au and Ag NCs [90, 91]. Similarly, in the synthesis of HYNCs by seeded-growth approaches or by co-injection methods, the control of reaction kinetics (temperature and mass gradients often in combination with the control of precursor reactivity)

has allowed the preferential growth of a shell or one-to-several domains onto the seed particles [28, 50, 92]

5.2 Chemical transformations at the nanoscale

Chemical transformations at the nanoscale, including the refinement of methods based on traditional corrosion techniques (the Kinkerdall effect and galvanic, pitting, etching and de-alloying corrosion processes) have been reported as effective tools for the production of advanced and exotic materials. Xia's group mastered the synthesis of metallic hollow NCs by widely studying the corrosion replacement reactions on single-component metal NCs. Galvanic replacement is achieved by reacting metals solutions (such as Au^{3+}, Pt^{2+}, and Pd^{2+} salts) with pre-formed NCs of a more reactive metal [83], producing, for instance, Au nanoboxes and nanocages from Ag nanocubes (Figure 3). The elemental Au produced in this reaction is confined to the vicinity of the template surface, nucleating into very small particles and growing forming a thin shell around the Ag template. These Au shells have morphologies similar to that of the Ag templates, with their void sizes mainly determined by the dimensions of the templates. Despite galvanic replacement reaction is the most versatile method of preparing hollow metallic nanostructures with controllable pore structures and compositions, the strategy has also been extended the production of hollow semiconductor [93] and oxide NCs [94].

The Kirkendall effect [95] results from the difference of the solid-state diffusion rates of the reactants in an alloying or oxidation reaction. A significant difference in the diffusion coefficients produce an accumulation of vacancies at the interface of the two components that can lead to the formation of cavities (Figure 3). Thus, the atomic diffusion occurs through vacancy exchange and not by interchange of atoms. Alivisatos and co-workers described the formation of hollow oxides (CoO) and chalcogenides (Co_3S_4) NCs through the Kirkendall effect employing Co NCs as a starting material and reacting them with oxygen and sulfur [96] while Cabot et al. studied the vacancy coalescence during the oxidation process of iron NCs leading to the formation of hollow NCs [82]. Worthy to mention is the work recently reported describing the sequential combination of both corrosion processes (galvanic and Kirdendall) which allowed the production of hollow NCs with sophisticated shapes and compositions [19]. The method, based on the attacking and pitting of preformed NCs from the "inside out", is scalable and performed at room temperature, and results in very complex geometric interconnected multicavity hollow NCs.

Similarly, chemical transformations *via* insertion or exchange of atoms reactions also provide new routes for the control of NC's morphology (Figure 3). In extended solids, reactions involving chemical exchange are in general very slow because of high activation energies for the diffusion of atoms and ions in the solid. However, it has been proved that cation exchange reactions can occur completely and reversibly in ionic NCs at room temperature with unusually fast reactions rates. A clear example is the interaction of CdSe with Ag^+ ions which yields Ag_2Se NCs, and vice versa, Ag_2Se reacts with Cd^{2+} ions to yield CdSe [18]. Similarly, CdSe NCs, has been transformed to ZnSe NCs via a sequence of two cation exchange reactions [97]. While this reaction is extremely fast (< 1 s) for NCs, similar experiments carried out with micrometer-sized powders of CdSe found the cation exchange to be virtually prohibited. This cation exchange reaction, initially investigated with Ag^+ ions, was easily extended not only to other cations but also to the formation of complex structures with precise structural and compositional tailoring [98–102]. Thus, CdSe NCs can be transformed into CuSe and PbSe though the cations exchange reaction with Cu^{2+} and Pb^{2+} ions while Au-CdS-CdSe core-shell-shell hybrid structures can be obtained from Au-Ag core-shell NCs [103].

Other post-synthetic transformations, such as thermal treatments [104, 105], irradiation by ion or electron beams [50, 106] or diffusion [44, 45, 50] are important to be considered in order to build complex NCs. Thus, it has been reported how an Au shell grown onto the surface of CdSe NCs migrates under exposure to an electron beam, leading to hybrid heterodimers. All of these examples also show that by making simple changes in the chemical environment of pre-formed NCs, it is possible to transform the process in a simple manner, allowing high yields and high consistency in composition and structure, and making the process particularly attractive for industrial applications as they are easily adapted to larger scales.

5.3 Use of pre-synthesized nanocrystals as catalysts and/or pure reagents

The use of pre-synthesized NCs as catalysts to promote the growth by seeded-growth methods is a synthetic strategy widely used to produce complex morphologies with high precision. Thus, the controlled nucleation of a second material exclusively at polar facets of NCs used as seed particles has been reported in the synthesis of nanowires of CdSe, InP, Si and Ge [107] and Au NRs [8] from semiconductor and metal seeds respectively. In the latter case, the reduction of the metal salt (first confined in metallomicelles and then in the surface of the seed NC) is typically carried out in an aqueous system in the presence of surfactants which

transport the Au ions to the growing seed NCs. Even more complex NCs, combining different materials in different morphologies, can be synthesized by taking advantage of this strategy reporting, for instance, the growth of Au domains onto CdSe NCs used as catalysts [28, 50].

Beyond the use of NCs as catalysts, they can be simply used as pure reagents (Figure 3). Due to their high surface-to-volume ratio NCs are especially reactive and by its dissolution one may provide electrons and ions suitable for the synthesis of secondary NCs in a suitable form. The strategy, similar to the use of sacrificial templates for the synthesis of hollow NCs, contains sophisticated differences such as the introduction of metallic traces in the form of Co NCs (used as electron and ion providers) into the synthesis of Pt NCs as an effective surfactant-independent mean of controlling Pt shapes [86, 87, 108]. It also illustrates the high susceptibility and mutability of the NC's shape to modification of the reaction kinetics during the early reduction process, and help progress toward a general mechanism for NC's shape control.

5.4 Combination of reducing agents and/or surfactant-assisted synthesis

The use of a combination of reducing agents that assist the temporal separation of nucleation and growth processes has been reported as an effective means of controlling the reactivity of metal precursors and therefore improving morphology and size-distribution of resultant NCs. By the use of different reducers at substoichiometric concentrations the nucleation and growth, and therefore the number and size of NCs in the reaction vessel, can be adjusted providing effective means for the control of the reaction kinetics [108]. Recently reported examples are the production of citrate-stabilized Ag NCs by the combined use of sodium citrate and tannic acid [91] and Au NRs through the use of salicylic acid and ascorbic acid [109].

Similarly, the surfactant-assisted synthesis has been also proved effective to control synthetic reactions. From the precursor to the final NC there are a series of intermediate states which reactivity can be modulated using organic molecules. Thus, the functional groups of surfactant molecules do not only interact (differently) with the NC's surface facets but also with the precursor and the reaction intermediate species that are present in the reaction. In this regard, a mean of tuning the reactivity of the precursor is the use of organic molecules which allow the complexation of precursor reagents and hence assist the growth or diffusion processes that otherwise cannot take place. This has been proved to precisely control the growth of a second material onto a metal and semiconductor seed NCs

with a large lattice mismatch [20, 38, 45, 50, 110] and the synthesis of multi-hollow NCs [19].

6 Post-synthetic considerations

Upon synthesis, a second challenge arises concerning the understanding of the combined or synergetic properties of the formed system. Thus, an important open question on the development of complex multi-component NCs relies on the complete understanding of how the morphology of the particle (how each material is grown with regard to the other) and how the domains are joined together (whether there is a bond between the materials, or they are brought together in close proximity using chemical linkers as by self-assembly). Additionally, when the synthesis is over, atoms at the surface may undergo diffusion process involving the coalescence of surface clusters at a single location, either on the surface of the NC or within the NC, which evidently can modify (often exhibit interesting deviations) the optical and electrical properties of these new multifunctional NCs. Known examples are the ripening process observed in metal-semiconductor HYNCs [45, 50].

Similarly, as a consequence of the high surface-to-volume ratio and low atomic surface coordination in NCs, degradation and dissolution processes may take place which are much more relevant at the nanoscale than in bulk materials. Thus, NCs are constantly exposed to degradation processes, which may either aggregate them into microscopic objects or reduce them to their constituent atoms either by chemical reactions with the surrounding media or easily because the degradated state is thermodynamically more favourable [111, 112]. This fact has important implications not only on the final NC's morphology and structure but also when studying its potential toxicity and safety, frequently related to the ability of NCs to release ions. Thus, degradation processes can lead to the morphological evolution of colloidal NCs (such as a broadening of the size distribution), following, for example, an Ostwald ripening process. Although degradation process is difficult to prevent, it is possible to protect NCs by designing engineered coatings. Thus, several studies show how the encapsulation of NCs in micelles or their functionalization with tight self-assembled monolayers (SAM) or antioxidant molecules could protect them from corrosion.

Last but not least, the viability (cost, safety and large scale production) of designed NCs has to be deeply studied. Toxicity and, particularly, ecotoxicity is also a major aspect of safety that has shown an increased interest while the public concern on environmental impact and sustainability of our resources has grown exponentially. From this perspective, TiO_2 and Ag NCs are by far the most indus-

trially produced and extensively studied in aqueous and soil ecosystems. In this case, to understand environmental fate, the evolution (such as aggregation and corrosion) of the NCs is critical. Those changes interfere with the properties of the NCs as well as their applicability (change of their properties). Additionally, sustainability (low impact on environment, energy efficiency of its production and uses) of the NCs is closely related to the feasibility of those NCs through the understanding of the energy cost of the NC's synthesis compare to the desire energy benefit obtain through their use in various applications. The design of room temperature synthesis which allows proper mixture of reagents before the reaction will be pursued to prepare the synthesis for scaling-up processes where thermal and concentration gradients can be a problem.

7 Conclusions

Despite the wide variety of synthetic strategies that have been reported for the production of advanced complex structures, including hybrid and hollow systems, the development of new synthetic strategies leading to a finer morphological control of NC's features is still a challenging task. Beyond the control of NC's morphology, one of the most important open questions is to understand how synthetic conditions can be controlled to combine several materials that may have very different structural and physical properties, and/or produce, for example, spatially arranged multi-hollow cavities, and do so while controlling the final NC's geometry.

Within this context, this review describes the way for designing a new generation of advanced NCs, summarizing the combination of different synthetic methods (kinetic control of the reaction, use of chemical transformations, use of pre-synthesized NCs as reagents, competitive reduction/oxidation of the precursors and surfactant-assisted synthesis) and post-synthetic processes (study and characterization of physico-chemical phenomena at the interface, chemical reactivity of the NCs, among others). As a result, these new synthetic principles could allow creating robust and easy-to-process NCs in a wide range of sizes, shapes and configurations that can be explored to achieve the combination of all degrees of control (material, size, shape and composition) in the synthesis of a new generation of advanced NCs which in addition of highly performant, are safe and sustainable.

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