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New Functional Ligands for the Preparation of Photoactive Nanoparticle-Based Materials

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A la meva mare

Whatever you do will be insignificant,
but it is very important that you do it.
Mahatma Gandhi

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ABREVIATIONS

3,5-dbcat	3,5-di-*tert*-butylcatechol
3,5-dbsq	3,5-di-tert-butylsemiquinone
A	Amplitude
AAC	Azide-alkyne cycloaddition
bix	1,4-bis((1H-imidazole-1-yl)methyl)benzene
C_0	Initial concentration of guest molecules
CHO	Chinese hamster ovary
CIN2	*Centre d'investigació en nanociència i nanotecnologia*
COSY	Correlation spectroscopy
CPP	Coordination polymer particles
d	Chemical shift
DBU	1,8-diazabicycloundec-7-ene
DEPT	Distortionless Enhancement Polarization Transfer
DIPEA	*N,N*-diiisopropylethylamine
DOS	Density of states
DOSY	Diffusion ordered spectroscopy
EDCI	*N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide HCl
E_{RET}	Ressonance energy transfer efficiency
EWG	Electrowithdrawing group
F_{fl}	Fluorescence quantum yield
HMBC	Heteronuclear multiple bond correlation
HOBt	Hydroxybenzotrialole
HOMO	Highest ocupied molecular orbital
HR-MS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
IR (ATR)	Infrared spectroscopy in attenuated total reflection
k_D	apparent diffusion constant
k_d	Surface erosion rate constant
l	Wavelength
LUMO	Lowest unocupied molecular orbital
m_{eff}	Effective magnetic moment
MOF	Metal-organic framework
MOM	Methoxymethyl ether
MPA	Mercaptopropionic acid

MTX	Methotrexate	R	Nanoparticle radius
NMR	Nuclear magnetic ressonance	R_0	Förster radius
NOESY	Nuclear Overhauser effect spectroscopy	r_{D-A}	Donor-acceptor distance
NP	Nanoparticle	RET	Ressonance energy transfer
OA	Oleic acid	r_{QD}	Quantum dot core-to-core distance
ODE	1-octadecene	SEM	Scanning electron microscopy
PBS	Phophate buffer solution	SPAAC	Strain-promoted azide-alkyne cycloaddition
PDI	N,N'-bis-(1-hexylheptyl)perylene-3,4:9,10-tetracarboxylic diimde	t	Photolminescence lifetime
PLQY	Photolminescence quantum yield	TEM	Transmission electron microscopy
PTDCI	N,N'-bis-(sec-butyl)-1,6,7,12-(4-tert-butylphenoxy)perylene-3,4:9,10-tetracarboxylic diimde	TOP	Trioctylphosphine
QD	Quantum dot		

Chapter I

Introduction

I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle. This field is not quite the same as the others in that it will not tell us much of fundamental physics [...] *but it is more like solid-state physics in the sense that it might tell us much of great interest about the strange phenomena that occur in complex situations. Furthermore, a point that is most important is that it would have an enormous number of technical applications. What I want to talk about is the problem of manipulating and controlling things on a small scale.*

Richard Feynman, Caltech, 1959,

"*There is Plenty of Room at the Bottom*"

I.1. NANOPARTICLES

Aiming for faster electronic devices with improved capabilities, more efficient diagnostic and therapeutic medical treatments or even cleaner energy resources, miniaturization has become one of the challenges of the new millennium. On the road to the fabrication of ever smaller products and materials, nanoscience and nanotechnology, the novel disciplines emerged at the end of last century, are playing a central role. Thus, inspired by Feynman's seminal lecture "*There is Plenty of Room at the Bottom*",[1] researchers in these areas have developed a wealth of techniques and strategies during the last decades that enable the study and manipulation of matter on the atomic and molecular scale. This has not only revolutionized the fields of physics, chemistry, electronics, and biology, but opened up the door to the rational design, synthesis and application of a variety of nanostructures and nanomaterials.[2]

Among them, the interest of this work lies in the field of nanoparticles (NPs). In particular, this dissertation focuses on the preparation of two different types of functionalized NPs (coordination polymer particles and quantum dots), the study of their properties, and their application in diverse fields (drug delivery and optoelectronics). Although a detailed introduction on each class of these systems will be provided in Chapters III and IV of the manuscript, a general overview of the synthesis, properties and applications of nanoparticles is given below.

Nanoparticles are atomic, ionic or molecular clusters of any shape with dimensions in the 1-100 nm range.[a] Nowadays they can be prepared from almost any material (e.g. metals, metal oxides, organic polymers), thus allowing their composition to be selected on the basis of the desired application.[2] Together with the very particular properties that they present, this has triggered enormous interest in the synthesis of nanoparticles and their use in many different fields.

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[a] Although this is the strict size definition of nanoparticles, other sub-micron particles with larger dimensions are often also considered as such. Actually, the coordination polymer particles developed in Chapter III of this thesis present diameters over 100 nm (~ 200 nm).

I.1.1. Synthesis of nanoparticles

The use of nanoparticles as inorganic dyes to stain glass and ceramics dates back to many centuries ago, as proven by the Roman Lycurgus cup exhibited in the British Museum.[3] In spite of this and the fact that Faraday already prepared a stable colloidal suspension of gold NPs in 1857,[4] the abilities to design and synthesize nanoparticles have been mainly developed during the last decades.

Currently, there exist two different approaches for the preparation of nanoparticles (and nanomaterials): the top-down and bottom-up strategies (Figure I-1). The former refers to the fabrication of smaller structures by reducing the size of bulk materials down to the nanoscale using external tools (e.g. cutting, milling, lithography, …).[2] Top-down procedures are able to produce highly regular nanoparticle sizes and shapes but the resulting materials often contain impurities and structural defects on their surface. In contrast, bottom-up methodologies start from smaller components of atomic or molecular dimensions that self-assemble together to give rise to larger and more organized systems. This approach enables the preparation of nanostructures with less surface defects and more homogeneous chemical composition.[2]

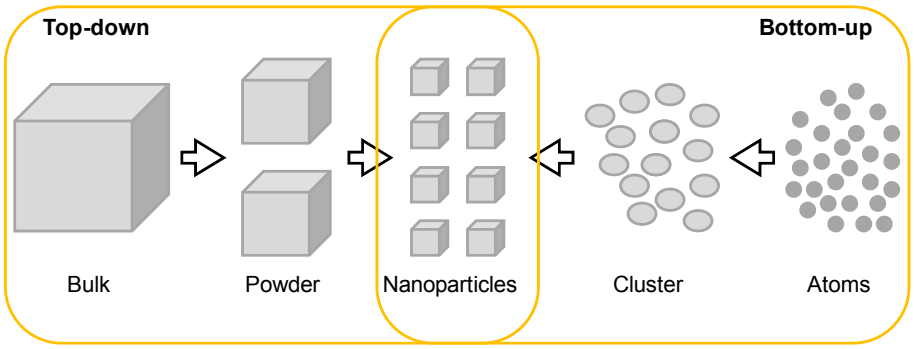

Figure I-1. Schematic representation of the two main approaches for the synthesis of nanoparticles: the top-down and bottom-up approaches.

Herein we have used bottom-up methodologies for the synthesis of coordination polymer particles and quantum dots, the two types of nanoparticles of interest in this work. In particular, both systems were prepared via homogeneous nucleation in liquid solution, a wet chemical process that proceeds via three main steps (Figure I-2A and B): (a) generation of a supersaturated solution of the atomic, ionic or molecular components of the nanoparticles, step I, (b) nucleation to form small clusters of these components, step II, and (c) subsequent growth of these clusters into nanoparticles, step III.[2] Briefly, when the concentration of a solute in a solvent exceeds its equilibrium solubility, the solution becomes supersaturated and possesses a high Gibbs free energy. The reduction of such energy is the driving force for the nucleation and growth steps, which only start once supersaturation reaches a certain value ($C_{min,nu}$) above the equilibrium solubility (C_S). Once nuclei are formed, nanoparticle growth occurs simultaneously. Actually, nucleation and growth

are inseparable processes above $C_{min,nu}$; however, they proceed at different rates. On the other hand, below $C_{min,nu}$ no more nuclei are formed and only growth processes take place until the concentration of the growth species decreases to the equilibrium concentration, finally yielding a colloidal suspension of the nanoparticles of interest.

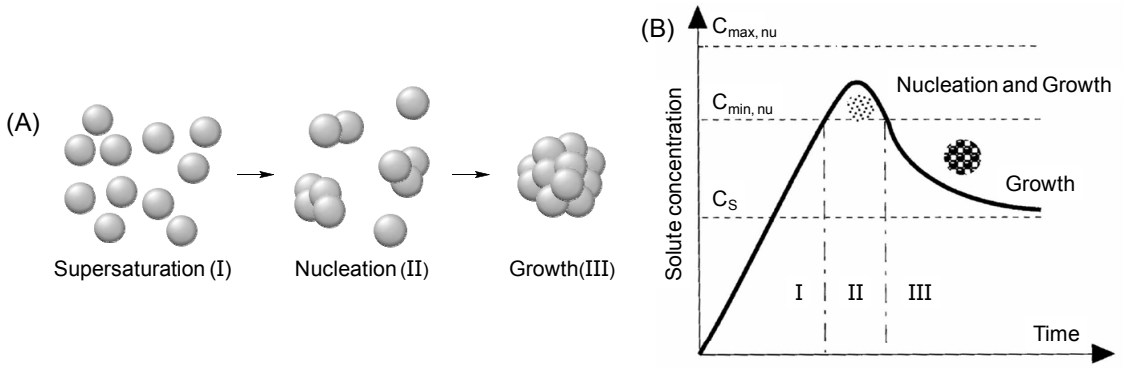

Figure I-2. (A) Three main steps for the formation of nanoparticles via homogeneous nucleation: supersaturation, nucleation and growth. (B) Schematic representation of these three steps in a solute concentration *vs* time graph.[2]

Owing to the high Brownian mobility and surface energy of sub-micrometer-sized particles, colloidal suspensions resulting from homogeneous nucleation are not expected to be stable. Instead, particle aggregation followed by precipitation of the large agglomerates formed should occur. To prevent this issue, stabilization strategies must therefore be followed during the wet chemical synthesis of nanoparticles, which rely either on their intrinsic surface properties or on the adsorption of a layer of molecular stabilizing moieties (capping layer).[5]

Generally, three different mechanisms can be responsible for the stabilization of nanoparticles in a liquid suspension: electrostatic, steric, and electrosteric stabilization (Figure I-3). Electrostatic stabilization arises from coulombic repulsion between surface-charged NPs, a situation that can be achieved intrinsically or upon introduction of small ionic stabilizers (e.g. citrate). In both cases, only kinetic stabilization of the colloidal suspension is achieved, which is highly dependent on the polarity of the solvent and the ionic strength of the medium. As such, electrostatic stabilization often fails for non-polar organic solvents, high electrolyte concentrations in aqueous suspensions, and/or long storage periods. This can be overcome by steric stabilization, which is based on the steric repulsion experienced by the organic capping layers of different particles when they are brought into close proximity. In this way, steric stabilizers act as spacers between the particles and thermodynamic stabilization is indeed achieved. Usually, steric stabilization is realized by the physi- or chemisorption of large hydrorcarbonated chains onto the surface of the particles (e.g. polymers). When such stabilizers additionally present ionic groups that are exposed to the outer surface of the particle, both electrostatic and steric effects occur and the colloidal suspension is said to be electrosterically stabilized.[5]

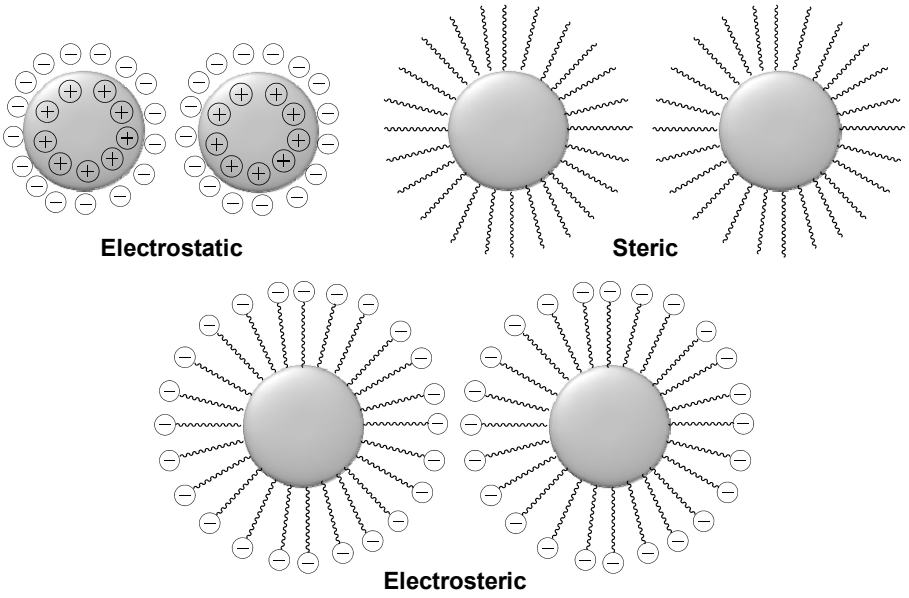

Figure I-3. Different strategies for nanoparticle stabilization: electrostatic, steric and electrosteric stabilization.

Although colloidal stabilization is the main function of capping layers, the organic molecules deposited onto nanoparticle surfaces play additional roles. First, they are involved in the control of nanoparticle growth, thus eventually influencing the size and polydispersity of the materials prepared.[2] On the other hand, they mainly determine the solubility behavior of the resulting particles.[6] As a consequence, exchange of the capping layer is required to ensure good dispersability when transferring nanoparticles from organic to aqueous media and vice versa. For instance, oleic acid-capped semiconductor NPs are only soluble in low dielectric constant organic solvents such as toluene, and they must be coated with polar molecules (e.g. mercaptopropionic acid (MPA)) in order to make them dispersable in aqueous medium for medical applications (Figure I-4).[7] Finally, incorporation of functional organic moieties to their surface may provide nanoparticles with new properties and applications, as it will be further discussed below.

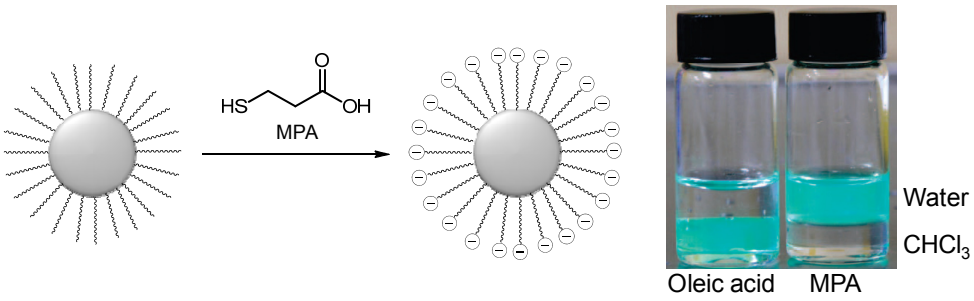

Figure I-4. Schematic representation of the process reported by Bae *et al.* for dispersing oleic acid-capped semiconductor nanoparticles in aquous media upon ligand exchange with mercaptopropionic acid.[7]

I.1.2. Properties and applications of nanoparticles

A number of different arguments explain the current interest in the preparation and application of nanomaterials. As already mentioned, optimization of many current technologies require miniaturization of the systems involved down to the nanoscale (e.g. transistors in an integrated circuit,[8] drug carriers for efficient cell intake via endocytosis[9]). In addition, nanoparticles and nanotubes can be used as fillers in nanocomposites, thus obtaining novel materials with improved mechanical, electrical or thermal properties.[10] However, from a basic science point of view, it is the special behavior that matter shows on the nanoscale what has attracted the attention of most researchers in the field of nanomaterials.[11]

An important factor that makes the physico-chemical properties of NPs be different from those of bulk materials is surface effects since they present higher surface to volume ratios.[11] For instance, a nanoparticle with a diameter of 10 nm possesses as much as 10 % of atoms on its surface, a percentage that scales up to 100% as nanoparticle size further decreases.[12] Since surface atoms present lower coordination numbers and cohesive forces, this results in clear changes in physical properties, such as lower melting temperatures.[11,12] From a chemical point of view, surface effects are exploited in the application of nanoparticles to catalysis, given the high intrinsic surface area that these materials present.[13] Indeed, the catalytically activity of nanoparticles has been demonstrated to be size dependent due to the larger relative amount of surface atoms as the material dimensions decrease.[14]

In addition, the physico-chemical properties of NPs are also strongly influenced by quantum effects, which do not play a significant role for larger scale materials.[11] By decreasing material size down to the nanoscale, bulk electronic bands with high density of states (DOS) become discontinuous and the occurrence of multiple well separated electronic states is observed, thus resembling the situation encountered for atoms and molecules. As such, bulk metals convert into semiconductor and insulator nanoparticles when the DOS turns to be so low as to create a non-negligible gap between the highest occupied and the lowest unoccupied electronic states.[11] Furthermore, electron motion is confined in nanoscale materials, which makes the actual electronic structure of the system be very sensitive to size changes.[11] The variation of energy bandgap in semiconductor quantum dots with nanocrystal dimensions is a very nice example of this phenomenon, which will be further discussed in Chapter IV. Chemical properties are also affected by quantum effects, as demonstrated by the size-dependent electron affinities[15] and redox potentials[16] of metal clusters.

Owing to the wide variety of chemical composition with which nanoparticles can be obtained and to the unique size-dependent properties that they exhibit nanoparticles have been proposed and applied in many different fields such as catalysis,[17] medicine,[18] electronics,[19] renewable energy[20] and photonics,[21] among others. Although all these applications benefit from the composition and small dimensions of the nanoparticles used, the incorporation of additional

molecular components to the system is often required to modulate its behavior and introduce novel functionalities. This is the case of the materials developed in this thesis, which consist of coordination polymer and semiconductor particles decorated with functional organic moieties for addressing specific applications.

I.1.3. Organic compounds for the functionalization of nanoparticles

The synergistic combination of molecular and nanoparticle properties in a single system allows the development of very versatile nanomaterials targeting highly demanding applications. In these materials, the functional molecules incorporated can be either loaded into the interior of the nanoparticles or attached to their outer surface. Multicomponent materials made of organic compounds embedded within nanoparticles are used in many different fields. In most of these cases, nanoparticles are used as carriers of the molecular moieties, which are the responsible to provide the system with a defined functionality. However, nanoparticles should not be considered as mere "molecular containers" in these materials, but they do often play an active role and are essential for the proper functioning of the system. For instance, mesoporous silica nanoparticles have been proposed as hydrophobic and hydrophilic drug carriers due to the large pore volume exhibited by these materials.[22] Drug release from these nanostructures has been modulated by the proper choice of polymer coating-shell, which improves their biocompatibility,[23] the controllable drug release[24] and the site-specific delivery into different tissues.

On the other hand, surface functionalization of nanoparticles with organic compounds is normally used to modulate their intrinsic properties, which are in this case determining the final application of the resulting multicomponent material. For instance, the surface of gold nanostructures for photothermal therapy can be functionalized with special antibodies to be selectively recognized by tumor cells.[25,26] Similarly, nanoparticles for drug delivery applications are often coated with poly(ethylene glycol) to increase their biocompatibility and to reduce thrombogenicity.[27] But functionalization of the nanoparticle surface is not only used for medical purposes, but also for modulating their optical, electronic and structural properties.[28] Thus, aggregates of colloidal gold nanoparticles can be formed by functionalizing their surface with complementary ssDNA sequences, which show different optical properties than the individual nanoparticles.[28a]

In this dissertation both types of multicomponent systems described above have been prepared and investigated. In Chapter III we report the synthesis of coordination polymer particles loaded with fluorescent ligands for the investigation of drug encapsulation and release from these metal-organic materials, an area of research that is attracting increasing interest nowadays.[29] In Chapter IV we explored a novel methodology for the controlled aggregation of semiconductor quantum dot nanoparticles via efficient and specific covalent bonding between their outer molecular capping

layers. If proven to be successful, this should allow the growth of novel nanomaterials for unidirectional energy and/or electron transfer in quantum dot-based photovoltaic devices.[30]

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CHAPTER II

Objectives

Two different projects have been developed in this PhD thesis involving the synthesis and characterization of novel materials based on the cooperative assembly of nanoparticles and functional organic compounds: coordination polymer particles loaded with fluorescent model drugs, and quantum dot semiconductor nanocrystals functionalized with reactive capping layers for controlled covalent assembly. Here we briefly describe the main goals devised for both projects.

II.1. New functional ligands for investigating drug release mechanisms from coordination polymer particles

During the last decades nanomedicine has emerged as a novel and promising discipline aiming at the application of nanotechnology to medical diagnostics and therapy. For instance, this is the case of nanoparticles, which are being proposed as smart carriers for controlled and selective drug release. In this work we were particularly interested in nanometer-sized coordination polymer particles as vehicles of organic therapeutic agents, which can be encapsulated into these materials via two different mechanisms: chemical bonding or physical entrapment. Even though different reports demonstrated the delivery of drugs incorporated via these two different approaches, no rational mechanistic studies of the release process had been conducted at the beginning of this thesis. In view of this, our first project consisted in the study of encapsulation and drug release mechanisms for amorphous coordination polymer particles (Figure II-1). With this aim, the following objectives were proposed:

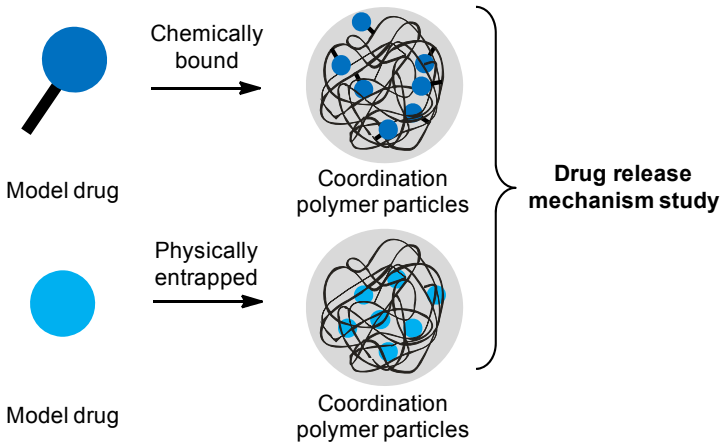

Figure II-1. Schematic representation of the main goal of the first project of this work: the study of drug release mechanisms from coordination polymer particles by synthesizing different model organic drugs that incorporate into these materials via distinct encapsulation processes (chemical binding and physical entrapment).

1. The design, synthesis and characterization of different fluorescent model drugs able to chemically bind to or physically incorporate into the matrix of coordination polymer particles.
2. The synthesis and characterization of coordination polymer particles bearing these fluorescent organic compounds.
3. The monitorization of the guest release profiles from these coordination polymer particles by means of optical measurements and their interpretation based on different mechanistic models for drug delivery.

A detailed description of the results obtained in these studies is given in Chapter III of this manuscript.

II.2. New functional ligands for quantum dot covalent assembly

Owing to their outstanding optical properties, quantum dot semiconductor nanoparticles have been proposed for different applications, ranging from (bio)chemical sensing and imaging to optoelectronics. Some of these applications, such as quantum dot-based solar cells and photonic wires, would enormously benefit from the controlled aggregation of quantum dots into defined nanostructures displaying efficient and unidirectional energy or electron transfer processes. This has motivated us to explore in the second part of this thesis the development of a new methodology for the preparation of controlled covalently-bonded heteroassemblies of quantum dots. As shown in Figure II-2, such methodology is based on the selective reaction between the ligands in the quantum dot capping layer via strain-promoted azide-alkyne cycloaddition, a rapid and efficient process that takes place in mild conditions and in the absence of metal catalysts. To attain this goal, the following objectives were devised:

1. The design, synthesis and characterization of different ligands for quantum dot binding bearing the reactive groups required to undertake the strain-promoted azide-alkyne cycloaddition process (azide and cyclooctyne).
2. The synthesis of different quantum dots and their functionalization with the reactive ligands prepared.
3. The preparation and characterization of covalently-bonded quantum dot heteroassemblies

The results obtained in these studies are described in Chapter IV of this manuscript.

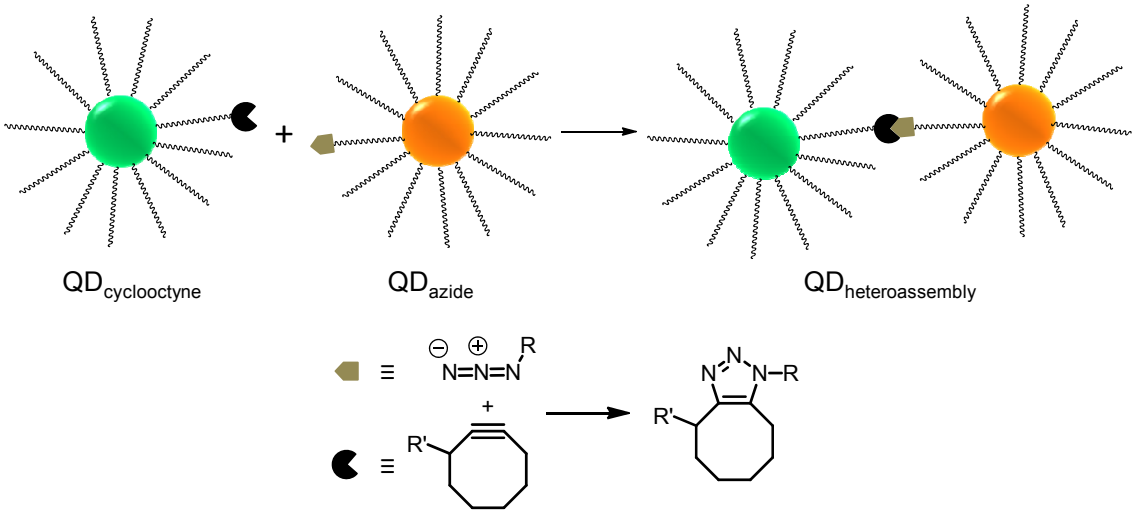

Figure II-2. Schematic representation of the main goal of the second part of thesis: the preparation of covalently-bonded heteroaggregates of quantum dots via strain-promoted azide-alkyne cycloaddition reaction between the ligands of their capping layers.

Chapter III

Unraveling Drug Release Mechanisms from Coordination Polymer Particles

Herein we investigate the release mechanisms from coordination polymer particles, which have emerged as new drug carriers in recent years. With this aim, different fluorescent organic molecules have been synthesized as model drugs that can be trapped into or tethered to coordination polymer particles and, consequently, be delivered via distinct processes -- namely, diffusion or particle degradation. By selectively monitoring the release kinetics of those fluorophores, we have not only demonstrated the occurrence of such mechanisms, but also assessed for the first time their individual efficiencies in view of the rational design of future systems with tailored drug delivery profiles.

Parts of this chapter have been published in: a) L. Amorín-Ferré, F. Busqué, J. L. Bourdelande, D. Ruiz-Molina, J. Hernando, F. Novio, *Chemistry* **2013**, *19*, 17508-17516. b) F. Novio, J. Simmchen, N. Vázquez-Mera, L. Amorín-Ferré, D. Ruiz-Molina, *Coord. Chem. Rev.* **2013**, *257*, 2839-2847.

III.1. INTRODUCTION

As well-known metal-organic frameworks (MOFs), coordination polymer particles (CPPs) arise from the interaction between transition metals and polydentate bridging organic ligands, which produces a network of metal-organic polymers that self-assemble into micro- and nanostructures.[1] CPPs are however amorphous materials, in contrast to crystalline MOFs, which have been widely studied for the last two decades and applied in different fields such as catalysis,[2] gas storage,[3] biomaging and medicine.[4] In spite of this, CPPs have emerged in recent years as an alternative to metal-organic frameworks for diverse applications. This is the case of drug delivery, the subject of interest in this chapter. Thus, CPPs have indeed proven to be excellent host matrices for different therapeutic agents due to the wide variety of compositions, sizes and shapes with which they can be obtained,[5] and their effectiveness as drug delivery systems has already been demonstrated *in vitro*.[6] Nevertheless, no drug release mechanisms have been rationally established to date for these carriers and fundamental studies of how the active molecules are embedded into and delivered from CPPs are still lacking. In view of this, we aim herein to design a novel strategy to thoroughly investigate the encapsulation and drug release mechanisms from coordination polymer particles.

III.1.1. Formation of coordination polymer particles

CPPs were first prepared by Mirkin *et col.* in 2005, which were composed of Zn(II) ions and the dicarboxylic ligand **1** (Figure III-1A)[7] Their synthesis proceeded through the two-stage process represented in Figure III-1B. Firstly, a salt of the metal ion selected (i.e. $Zn(OAc)_2$) was mixed with the ditopic organic ligand chosen to form the corresponding coordination polymer; secondly, addition of a poor solvent to the mixture provoked aggregation of the polymer chains and rapid precipitation of micro- or nano-CPPs. Although other strategies have been developed for the

formation of CPPs, such as microemulsion techniques[8] and solvothermal synthesis,[9] the solvent-induced precipitation methodology developed by Mirkin *et col.* still remains the most commonly used due to its simplicity.

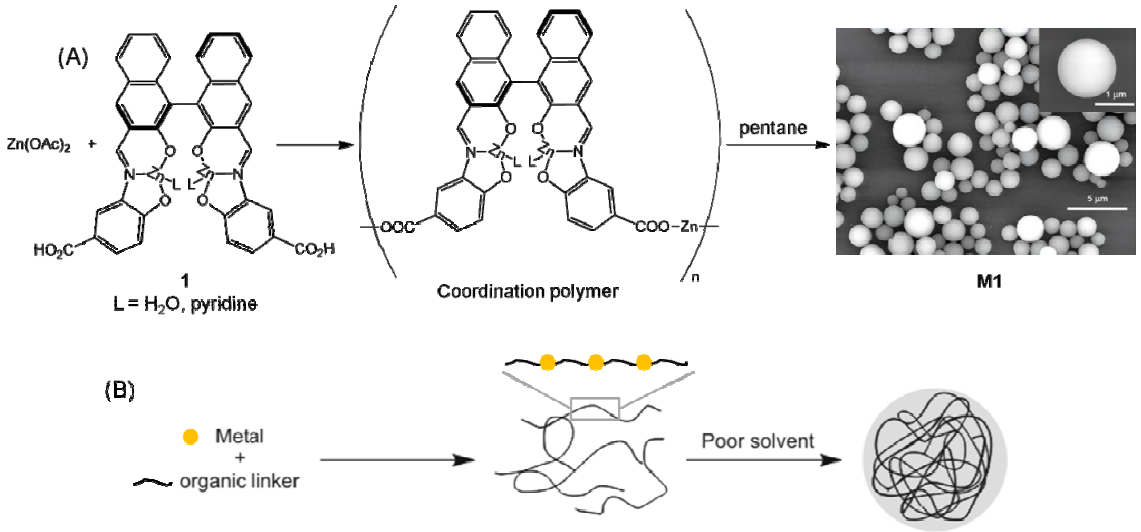

Figure III-1. (A) Formation of Zn-based CPPs synthesized by Mirkin *et col.*[7] (B) Schematic representation of the two-step process designed for the formation of these CPPs, which relies on the introduction of a poor solvent to the mixture of the metal ions and organic ligands selected.[7]

By means of time-resolved scanning electron microscopy (SEM) measurements, Mirkin *et col.* investigated in detail how CPP formation and growth proceed in their synthetic approach and proposed a mechanism involving six different steps (Figure III-2): (i) formation of individual coordination oligomers that further react to yield (ii) small seeds and (iii) seed aggregates, which subsequently (iv) fuse, (v) grow and finally (vi) anneal.[10] While the main driving force of stages (i-iii) has been ascribed to the formation of new coordination bonds between metal ions and ligands dispersed in solution, at the ends of the polymer chains and in the surface of the seeds generated, the reduction of the surface tension of the nano- and microstructures created mostly accounts for steps (iv-vi). Similar growth mechanisms have been proposed for the synthesis of CPPs presenting different morphologies, such as the coordination polymer nanocubes reported by Jung *et al.*[5]**¡Error! Marcador no definido.**[b]. Thus, they observed the formation of polymer nanowires as initial seeds that then self-assembled into cubic agglomerates, which finally annealed to form nanocubes with smooth surfaces. As such, the growth mechanism first described by Mirkin *et col* has now become well-accepted to account for the synthesis of a wide variety of CPPs.

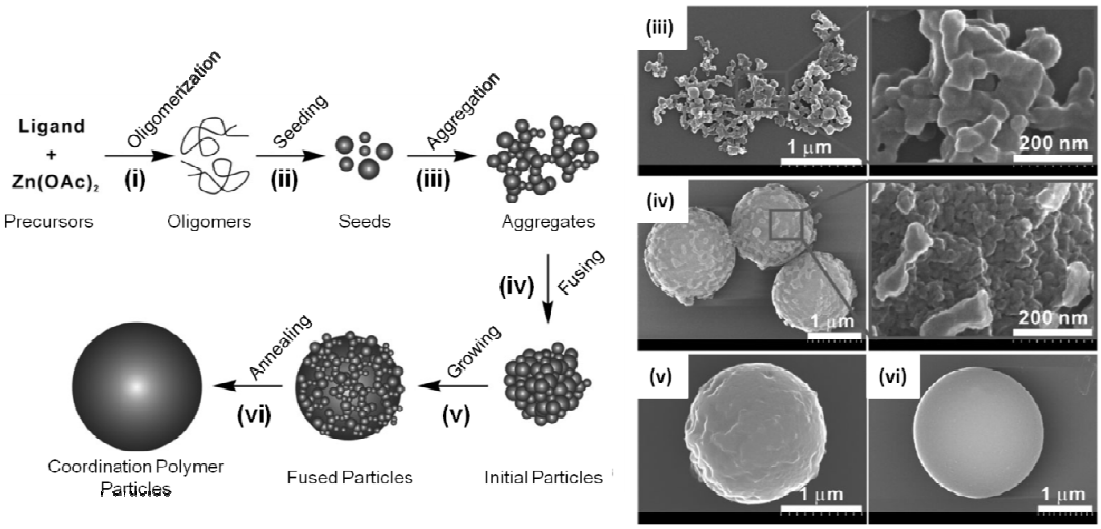

Figure III-2. Proposed mechanism of formation of CPPs by Mirkin *et col*., which involves six different stages. SEM images corresponding to steps (iii-vi) of this mechanism are shown on the right part of the figure.[10]

III.1.2. Properties and applications of coordination polymer particles

Functional CPPs can be obtained from a wide variety of metal ions such as Zn(II),[7,10] Pt(II),[11] Au(III),[12] La(II),[13] Gd(III),[14] and Co(II),[15] among others, in combination with different organic linkers. Actually, owing to the almost limitless choice of metal centers and organic ligands, the physico-chemical properties of CPPs can be easily modulated by proper selection of its constituent building blocks, thus enabling a number of different applications to be addressed by simply changing the composition of the system. For instance, Mirkin *et col.* demonstrated that the optical behavior of CPPs composed of divalent transition metals and a binapthyl bis-metallotridentate Schiff base could be tuned by changing the nature of the metal ion (Zn(II), Cu(II), Mn(II) and Pd(II)), which allowed the preparation of materials displaying different colors and emissive properties (Figure III-3).[5a] Noticeably, all these different materials were obtained from initial Zn-based particles via partial ion exchange processes, which resulted in CPPs with very similar sizes and shapes. This therefore proved that the variation in optical properties of these systems could be mainly attributed to the change in their composition.

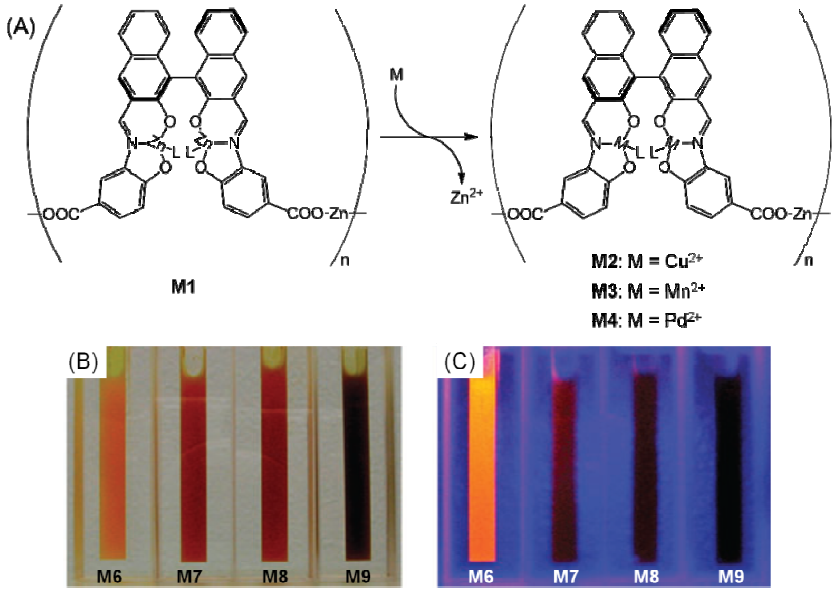

Figure III-3. (A) Preparation of different CPPs between divalent transition metals and a binapthyl bis-metallotridentate Schiff base via total ion exchange of Zn-based particles. Changes in (B) color and (C) luminescence of the resulting materials.[5a]

Alternatively, magnetically active metal ions can be used to prepare coordination polymer particles displaying functional magnetic properties.[15,16] This is the case of the Co-based CPPs reported by Ruiz-Molina *et col*,[15] which used the flexible linker 1,4-bis((1*H*-imidazol-1-yl)methyl)benzene, **2**, the coordinating ligand 3,5-di-*tert*-buthylcatechol, **3**, and a cobalt precursor to obtain amorphous coordination polymer particles (Figure III-4A). The resulting material exhibited different magnetic moments when increasing temperature due to the existence of distinct electronic isomers (the so-called "valence tautomers"). This effect was ascribed to a thermally-induced electron transfer process from the catechol group to the metal ion, which resulted in oxidation of the ligand to its semiquinone form and reduction of the initial low spin Co(III) center, *ls*-Co(III), to the high spin Co(II) species, *hs*-Co(II), (Figure III-4B).[17] Such magnetic switching behavior, which had been known for long for discrete cobalt coordination compounds,[18] can therefore be transferred to CPPs by properly selecting the nature of the organic ligands involved. In this chapter we have chosen this type of Co-based amorphous particles as the system of reference to investigate drug encapsulation and release mechanisms from CPPs.

Aside from composition-dependent properties, the size of CPPs can also be finely tuned by adjusting the experimental conditions of the synthetic procedure. In particular, the size of the resulting particles depends on three main parameters when using the solvent-induced precipitation method: (a) the nature of the poor solvent, which was exploited by Mirkin *et col.* to obtain Zn-based coordination polymer micro- and nanoparticles from the same initial reaction mixture by adding apolar pentane and polar diethyl ether, respectively;[7] (b) the rate at which the poor solvent is added; and (c) the reactant concentration ratio used. The effect of the two last parameters has been deeply investigated by Ruiz-Molina *et col.* and in collaboration with our group. On one hand, it was shown

that smaller Co-based CPPs could be prepared by decreasing the addition rate of the poor solvent;[15] on the other hand, we have demonstrated that mixing different concentrations of reactant precursors yielded Zn-based CPPs with distinct sizes.[19]

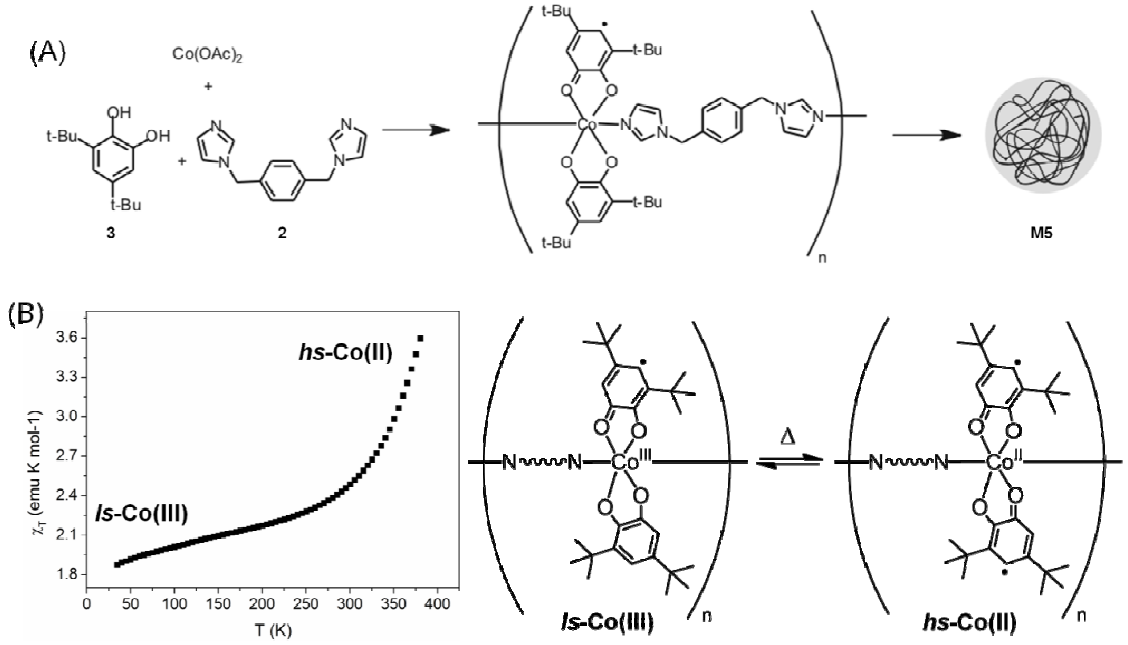

Figure III-4. (A) Formation of magnetically-active, Co-based CPPs with ditopic linker **2** and catechol **3**. (B) Thermal variation of the magnetic moment of the resulting particles as a result of their valence tautomerism behavior, which makes their metal ions turned from *ls*-Co(III) to *hs*-Co(II) states due to intramolecular metal-ligand electron transfer upon increasing temperature.[15]

Regarding shape of CPPs, to date there is not a rational explanation for morphology regulation. CPPs have been synthesized as micro-[7] and nanospheres,[15] microcubes,[5b] microrods[20] and even as wheel structures.[5c] Moreover, Jeon *et. al.* reported the reversible conversion between different shapes of same chemical composition CPPs by modifying the precipitation solvent.[21] In particular, amorphous spherical Zn-based CPPs were converted into crystalline rod-shape structures by the addition of methanol upon the dried material. The reversible process was achieved after adding a mixture of pyridine/diethyl ether, which interconverted the crystalline rod-shape structures into the initial spherical forms.

Because of the nearly unlimited modulation of the CPP properties that can be achieved by tuning their composition, size and shape, these materials have been proposed and applied in several different fields such as catalysis,[22] gas storage,[23] bioimaging[24] and medicine[25]. Herein we are mainly interested in the last of these applications and, in particular, in their use as drug delivery systems. Accordingly, next section gives an overview of previous reports where CPPs have been exploited to encapsulate and release therapeutic agents.

III.1.3. Drug encapsulation and release from CPPs

Three different strategies have been applied for the encapsulation of drugs into CPPs for medical applications: (a) the use of a pharmacologically-active metal ion to directly form the coordination polymer particles, such as cupper or platinum ions;[25a,b] (b) the use of an active organic drug as one of the building blocks of the CPPs,[25c,d,26] and (c) the encapsulation of the drug physically within the particles without being chemically tethered to the polymer scaffold.[25e,f] Owing to the larger number and versatility of organic drugs, in this work we have focused on the two last methodologies.

III.1.3.1. Chemical linkage of the drug

There exist several organic drugs that contain heteroatoms able to coordinate metal ions (e.g. oxygen, phosphorous, sulfur and nitrogen atoms), which therefore can be exploited for chemical attachment to the polymer scaffold of the CPPs. In this case, drug delivery can only take place via particle degradation, which takes profit of the inherent instability of most coordination polymers at physiological conditions. As an example, Huxford *et al.* used methotrexate (MTX) as bridging ligand to form Gd-based CPPs (Figure III-5A).[14] MTX is a small-molecule chemotherapeutic agent, which contains carboxylate moieties able to coordinate Gd(III) ions. Once prepared, MTX release from Gd-based CPPs was observed to be completed after *ca*. 40 hours in phosphate buffer solution (PBS, pH = 7.4) at 37 ºC, and it was attributed to CPP degradation in the physiological medium used (Figure III-5B).

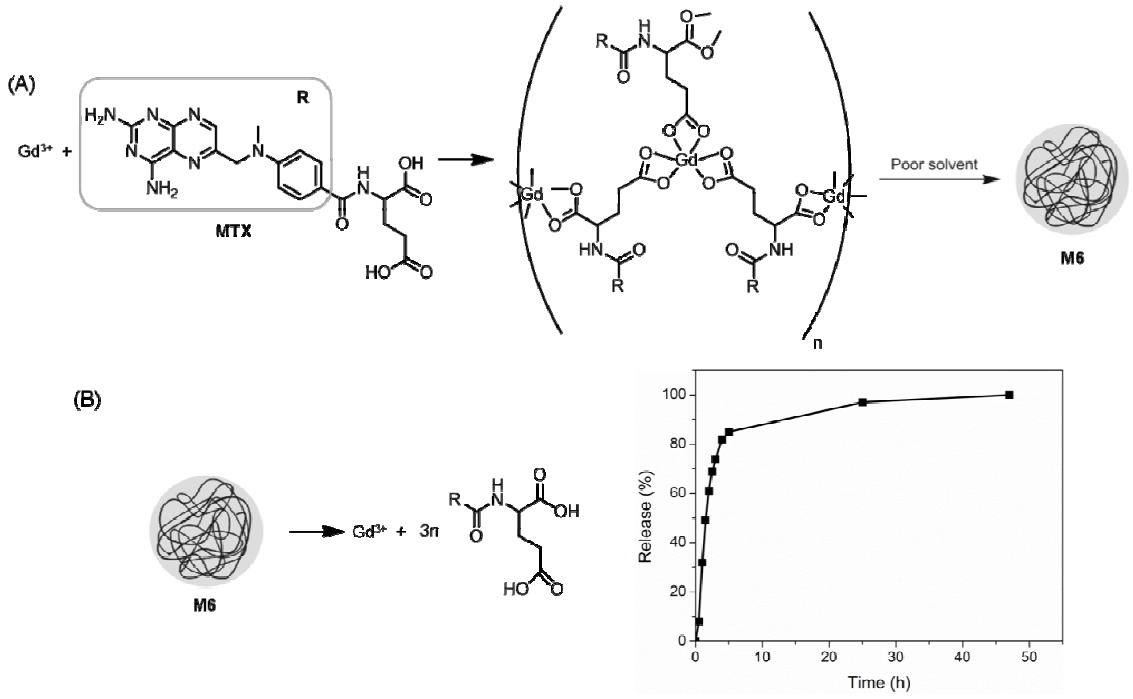

Figure III-5. (A) Gd-MTX coordination polymer and CPP formation. (B) MTX release from the resulting CPPs due to particle degradation.[14]

Similar results were reported by Xing *et al.*, who followed two different strategies for the formation, and subsequent drug release studies, of different metal-based CPPs containing distinct fluorescent anticancer drugs able to coordinate metal ions, such as MTX and alizarin red S.[27] As depicted in Figure III-6, the first route consisted in the direct reaction between the metal ion precursor and the drug, which was the only bridging ligand used. The second approach consisted in the polymerization of these two components together with an additional co-bridging ligand (e.g. polyethyleneglycol). Drug release was investigated for Fe-, Co-, Zn- and Cu-based CPPs formed by both routes, which allowed concluding: (a) as reported by Huxford *et al.*,[14] most drug-loaded particles were observed to slowly release its cargo at physiological conditions, which was ascribed to CPP degradation arising from disruption of metal-ligand bonds; (b) since the stability of most of these bonds is very sensitive to pH, changes in the acidity of the medium could be used to modulate the kinetics of drug delivery; (c) the use of co-bridging ligands with designed pH-dependent affinities towards metal ions was found to be crucial in those cases where the stability of the drug-metal coordination bond was observed to be too high or too low for practical applications in drug delivery via CPP degradation.

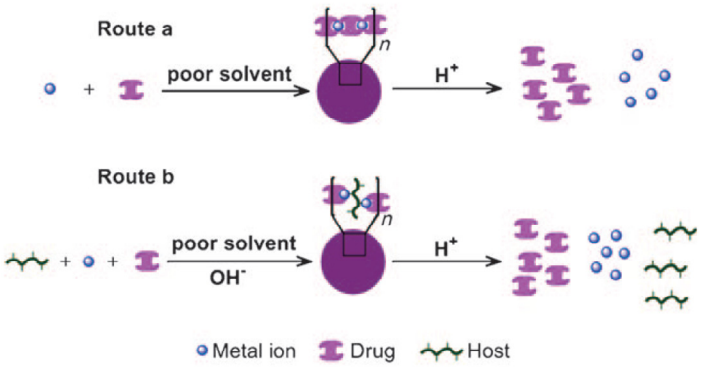

Figure III-6. Two different strategies followed by Xing *et al.* for the incorporation of a coordinating drug into CPPs, which involves the use (b) or not (a) of co-bridging ligands. In both cases, the kinetics of drug release could be controlled by means of the acidity of the medium due to the pH-dependent stability of the metal-ligand coordination bonds exploited.[27]

Even though pH-controllable, complete release via coordination polymer degradation has been demonstrated for drugs chemically tethered to CPPs ,no in-depth mechanistic studies of the encapsulation and delivery processes have so far been reported. For instance, this would be required to assess the efficiency of drug incorporation by coordination to metal ions, since a fraction of the loaded active molecules might be simply physically entrapped within the CPPs instead of chemically bonded, thus critically affecting the kinetics of drug delivery. Thereby, a comprehensive study of drug encapsulation and release is needed to fully exploit the advantages of CPPs as micro- and nanocarriers of therapeutic agents. Aside from drugs with metal coordinating properties, this study should also be expanded to other active species without chelating capacity, which should be encapsulated into and released from CPPs via different mechanisms. Owing to the porosity of these

materials,[5a] mechanical entrapment into the coordination polymer network is the best alternative, from which the drug could be delivered by simple diffusion processes.

III.1.3.2. Encapsulation via physical entrapment

In collaboration with Ruiz-Molina *et col.*, our group has reported first examples of encapsulation of active drugs within CPPs via physical entrapment. In particular, our attention focused on fluorescenct anticancer drugs such as doxorubicin, SN-38, camptothecin and daunomicin, which were embedded into Zn-based CPPs prepared using **2** as bridging ligand (Figure III-7A).[25e] Nearly complete drug delivery was achieved in 40 hours for these materials, which displayed very similar release profiles regardless of the active species encapsulated (Figure III-7B). Although no extensive mechanistic studies were performed, we attributed drug release from these CPPs to the combination of three different processes: desorption from the surface of the particles, diffusion through their pores, and particle degradation. The lack of detailed knowledge of the complex interplay between these different mechanisms has motivated the investigation on drug encapsulation and release processes undertaken in this chapter, with which we aim to enable the design of future CPPs with tailored delivery kinetics of their encapsulated active species.

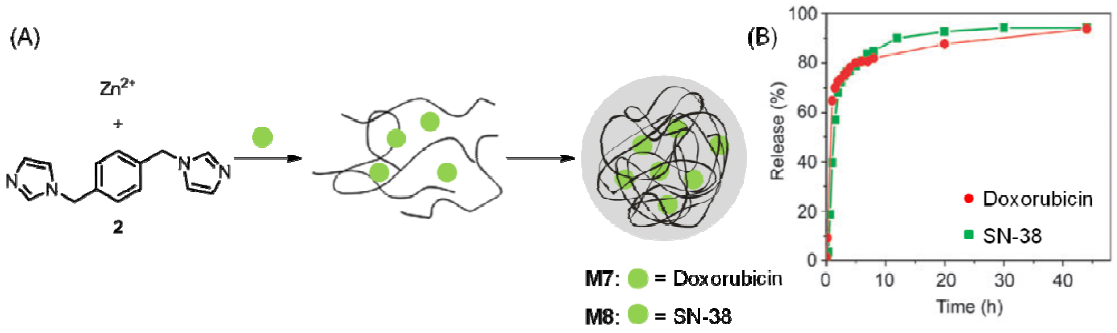

Figure III-7. (A) Schematic representation of the drug encapsulation strategy followed by Ruiz-Molina *et col.*[25e] (B) Drug release profiles of doxorubicin (green) and SN-38 (red) from the resulting Zn-based CPPs.

III.1.4. Fluorescent guests as drug models for encapsulation and release studies

As introduced in the previous sections, drug release from CPPs can take place via three different mechanisms: (a) fast, undesired desorption from the surface of the particles, which gives rise to the so-called *burst effect* (i.e. sudden release at t~0), (b) diffusion through the pores of the material, and (c) slow coordination polymer degradation due to the limited stability of metal-ligand bonds in aqueous media. In this chapter we have focused on the investigation of the last two processes, which must control drug delivery from CPPs provided that unwanted desorption is prevented by proper surface rinsing prior to their use. Noticeably, the delivery kinetics associated to diffusion and degradation processes are expected to be largely different, thus allowing rational

design of the time-dependent drug release profile from CPPs by selecting one of these two mechanisms or an appropriate combination of both. This does not only requires a thorough separate analysis of the kinetics of diffusion- and degradation-controlled drug delivery, but also accurate control of the encapsulation process, which will eventually determine the actual release mechanism(s). Thus, while active molecules chemically-tethered to the CPP scaffold by coordination bonds must be delivered via particle degradation, both diffusion and degradation processes should account for the release of mechanically entrapped drugs.

In view of this, a novel strategy has been developed in this work to undertake a comparative study of both types of encapsulation and release mechanisms for CPPs. summarizes the main guidelines of our approach, which presents the following key aspects:

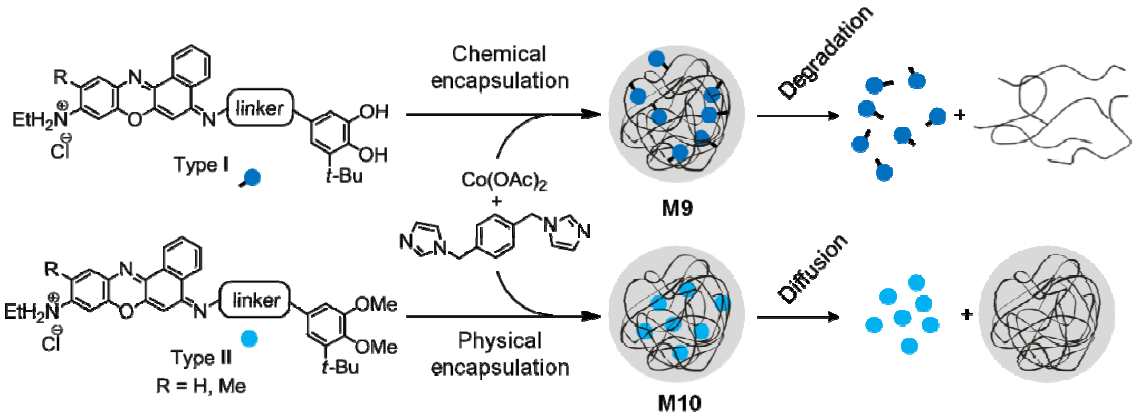

Figure III-8. Schematic representation of Co-based CPP formation with model fluorescent drugs of types **I** and **II**, with which different drug encapsulation and release mechanisms are expected to be induced.

1. The use of luminescent ligands as drug models to enable monitorization of their release from CPPs by means of fluorescence spectroscopy, which is a very sensitive technique that allows analyte detection at very low concentrations and even down to the single molecule level.[28] In particular, we chose benzophenoxazine dye derivatives as the fluorescent core of our ligands, since they (i) present high luminescent quantum yields, (ii) emit in the red region of the visible spectrum and, therefore, are suited for selective fluorescence detection, and (iii) can be functionalized in a rather straightforward manner.
2. The preparation of two families of ligands (type **I** and **II**) by tethering the benzophenoxazine fluorescent unit to a *t*-butylcatechol moiety. Type **I** ligands present free, unprotected catecholic hydroxyl groups, which should enable coordination to the metal ions selected for the formation of the CPPs. As such, type **I** ligands are expected to be chemically encapsulated within these materials. By contrast, the hydroxyl moieties of the catechol unit of type **II** ligands are to be protected as methoxymethyl ether groups, thus preventing metal coordination. Consequently, this class of ligands could only be incorporated into the polymer matrix of the CPPs by purely mechanical entrapment.

3. The synthesis of Co-based CPPs from type **I** and **II** ligands and co-bridging linker **2** by means of the solvent-induced precipitation method developed by Mirkin *et col*.[7] This class of coordination polymer particles was selected for several reasons. First, some precedents had already been reported describing the successful formation of amorphous CPPs from Co ions, bridging ligand **2** and coordinating *t*-butylcatechol molecules.[15] This will therefore provide us with a simple way to incorporate the type **I** fluorescent guest to the polymer backbone in **M9** without modification of the coordination sphere of the metal ion. Second, the coordination compounds composed of Co ions, catechols and *N*-bonded ligands display absorption spectra that expand all over the visible spectrum.[17] Therefore, they should quench the emission from the encapsulated type **I** and **II** ligands via resonance energy transfer (RET,[29] see section III.2.4). As a result, these ligands should turn fluorescent and, therefore, be selectively detected only after release from the CPP host. Third, valence tautomerism is expected for this type of particles, as previously demonstrated.[15] In this work, we aim to take advantage twice of this property: (a) to assess the structural differences between amorphous CPPs prepared from type **I** and type **II** ligands, since the temperature range at which the transition between the two electronic isomers of the system occurs is very sensitive to the structure and local environment of the coordination complex; and (b) to modulate drug delivery kinetics by means of temperature changes inducing the interconversion between the two valence tautomers of the system. Such tautomers present different electronic configurations, metal ion oxidation states and metal-ligand distances,[18b] which may influence both the diffusion and degradation processes of release.
4. The investigation of the release of type **I** and type **II** ligands from **M9** and **M10**, which we have designed as benchmark systems for the separate analysis of degradation- and diffusion-controlled drug delivery, respectively. Thus, chemically-tethered type **I** ligands must only be released from **M9** via degradation processes. In the case of **M10**, type **II** guests should be mainly delivered by diffusion provided that particle degradation takes place in a longer time scale. In addition, the effect of temperature and, therefore, valence tautomerism interconversion in those release mechanisms would also be studied.