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Stéphane Gineste, Christophe Mingotaud

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Double-hydrophilic block copolymer–metal ion associations: structures, properties and applications

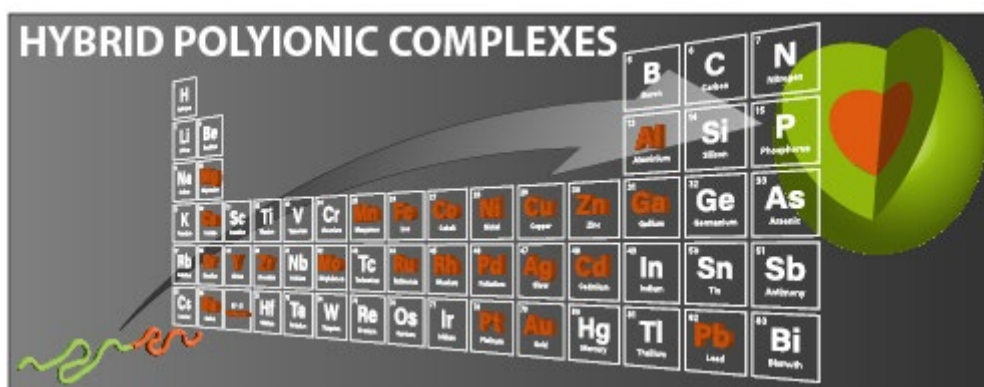
Stéphane Gineste, Christophe Mingotaud*

Laboratoire des IMRCP

CNRS UMR 5623, University of Toulouse, Université Toulouse III - Paul Sabatier
118, route de Narbonne 31062 Toulouse Cedex 9, France

* Corresponding authors:

C. Mingotaud: christophe.mingotaud@univ-tlse3.fr, Tel: +(33) 561558696



Abstract

Hybrid polyionic complexes (HPICs), constructed from double-hydrophilic block copolymers and metal ions, have been largely developed with increasing interest in the past decade in the fields of catalysis, materials science and biological applications. The chemical natures of both blocks are very versatile, but one block should be able to interact with ions, and the second one should be neutral. Many metals have been used to form HPICs, which have, in their simplest architectural form, a core-shell structure of a few tens of nanometers in radius with an external shell made of the neutral block of the copolymer. In this review, we focus our discussion on the stability, shape, size and inner structure of these hybrid micelles. We then describe the most recent applications of HPICs, as reported in the literature, and point out the current challenges, missing structural information and future perspectives for this class of organized structures.

Keywords: micelle, vesicle, DHBC, copolymer, metal ion

1. Introduction

Numerous studies have addressed the self-assembly of amphiphilic compounds, such as surfactants or copolymers. In water or other polar solvents, these molecules or macromolecules aggregate, leading to well-defined structures, such as micelles, worm-like micelles, vesicles or more complex lyotropic phases.[1, 2] Applications of such architectures range from day-to-day life to various scientific fields, from material science to medicine.[3] The so-called “hydrophobic effect” is the driving force for such aggregation. [4] This effect cannot be applied to purely hydrophilic compounds without hydrophobic groups, but electrostatic interactions may then be used to trigger association. Indeed, oppositely charged polymers spontaneously self-assemble when mixed together, leading to complex coacervates.[5-7] Micelles, vesicles and denser nanoparticles are then constructed by coulombic interactions combined with the release of counterions and bound water molecules, resulting in entropy gain. Typical sizes of these objects are between a few tens to hundreds of nanometers.

In recent decades, the development of polymer chemistry has led to macromolecules with ever more precise and controlled chemical structures as well as lengths. Among all the synthesized hydrophilic polymers, double-hydrophilic block copolymers (DHBCs) have attracted increasing attention.[8, 9] Corresponding to an easy and well-controlled synthesis, the gold standard among DHBCs is a linear copolymer formed by a neutral poly(ethylene oxide) block linked to a second ionic block made of poly(acrylic acid). Many DHBCs have been synthesized with various structures, chemical compositions, and properties (such as stimuli-responsive macromolecules). The potential of DHBCs is now well recognized, including the ability for some of them to self-assemble when dispersed in solution, leading, for example, to vesicles.[10] Mixing DHBC with a polymer of the opposite charge can trigger micellar polyelectrolyte association.[11] The presence of the neutral block usually limits the size of the aggregates and increases the colloidal stability of the final structures, which have a size between a few to hundreds of nanometers.[12]

To generate coulombic interactions and therefore the self-association of DHBCs, simple multivalent metal ions can be used instead of a second ionic polymer. To our knowledge, K. Kataoka[13] was the first to report in 1996 such aggregation of a DHBC (namely, poly(ethylene oxide)-*block*-poly(aspartic acid)) through interactions with platinum ions (in the form of cisplatin), leading to polymeric micelles with an average diameter of 16 nm. Shortly thereafter, M. Antonietti et al.[14] also demonstrated that the interactions of poly(ethylene oxide)-*block*-poly(ethyleneimine) with noble metal ions (gold, palladium...) formed micellar structures that did not exist without the metal. Although DHBC properties and aggregation have been largely reported and summarized in the past few years,[8, 15] no review on such metal-DHBC associations has been published to provide researchers with a complete perspective of the already studied systems and their properties.

The present review attempts to fill this gap by discussing the different systems reported in the literature, pointing out the main parameters controlling metal ion/copolymer associations and showing their various properties and applications. The highlighting of the remaining questions and challenges will be made throughout this review to emphasize the future potentials of these structures.

Metal-mediated DHBC self-assemblies are called complex coacervate core micelles, block ionomer complex micelles, polymeric metallosomes or hybrid polyionic complexes (HPICs). This last abbreviation will be used in this review to denote all metal/DHBC associations regardless of their final structures (micelles, vesicles or large nanoparticles). We will first review the chemical structures of the systems reported in the literature, analyze HPIC formation, describe the various architectures of these associations and then focus our attention on their potential applications.

2. The various HPIC systems

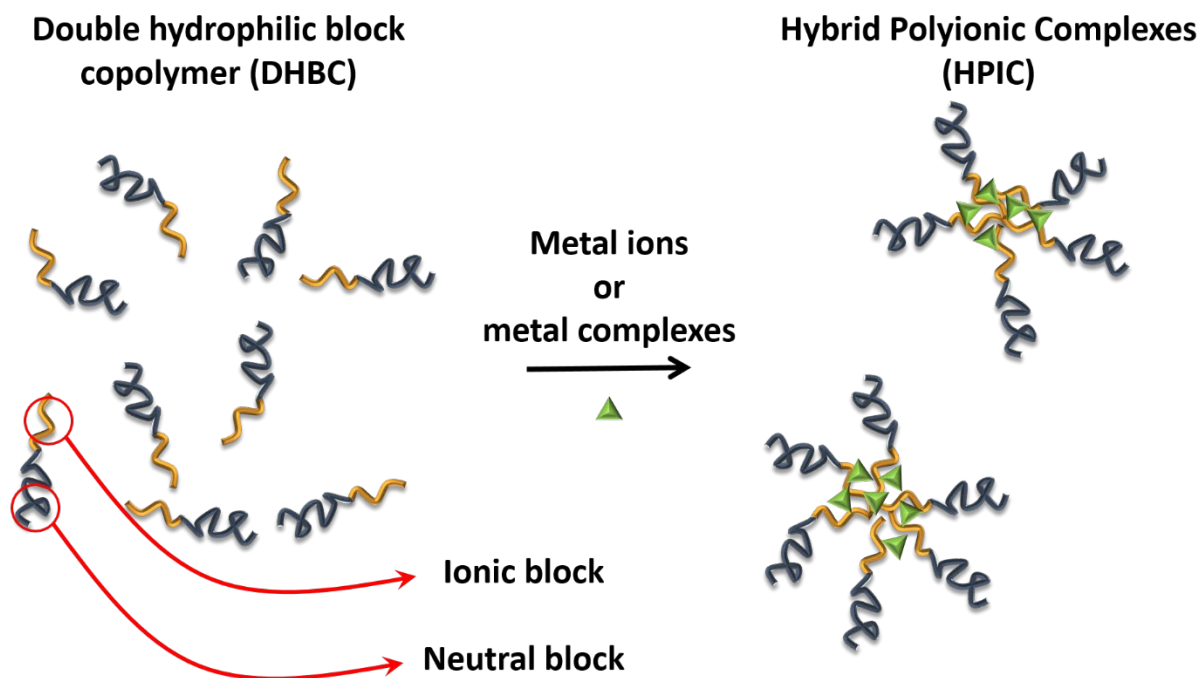
In the literature, many examples of soft matter organized systems have been designed and described to include metal ions. For instance, gels made with or thanks to metal ions have been largely studied [16-19] but also simple bulk polymers interacting with various metallic cations.[20-22] This was particularly developed with ionic polymers for membrane filtration.[23, 24] Thermotropic [25-27] or lyotropic[28-30] liquid crystals have been also based on metal ions or complexes. For aqueous dispersed systems, simple polymers[31, 32] or biopolymers[33] can interact with metal ions, stabilize and transport them. Small molecules such as surfactants and in particular metallosurfactants,[34] possibly organized as micelles[35-37] or vesicle[38-40] have been also extensively studied to capture, extract or stabilize metallic species in solution. A tremendous number of examples of dispersed colloids[41], or nanoparticles[42, 43] can be also found in the literature demonstrating that hybrid systems made of inorganic materials and soft matter can be readily available with a large panel of properties and applications.

Compared to the previous systems, the HPICs have numerous advantages. As shown in the next scheme, the main benefit of the HPIC system is the ease to build them just by mixing metal ions and a copolymer with often simple chemical architecture (and therefore synthesis). This is strongly different from metallosurfactants, liquid crystal or even specific polymers which may require long organic synthesis of the elemental bricks constituting the final soft matter systems. Also, the HPIC formation process is easily transposed to a large number of metal elements, leading to colloids stable (by design) in water. By comparison, dispersion of nanoparticles is often much more difficult, since their synthesis pathway is strongly related to the nature of the final material. Furthermore, the colloidal stability of the nanoparticles depends on the ligands on their surface, ligands which may require to be exchange (with difficulties) in order to get water-compatible nanoparticles.

The chemical stability of the HPIC depends mainly on the nature of the metal ions and the complexing functions of the DHBC copolymers. This is easily adjustable to release (or not) the metal ions at will. This adjustability is due to the total decoupling between the choice (and synthesis) of the organic and inorganic part of the elemental brick constituting the final HPICs. On the contrary, the soft matter systems designed to disperse metal ions are often based on specific ligand and molecules/macromolecules making the final system less adjustable. Mixing polymers or metal ions could also help modulating the HPIC properties, in a much easier way than with nanoparticles or bulk systems.

Finally, as described in the following parts, the (minimum) size of the HPICs and their low dispersity in size is somewhat independent of the composition, when dispersed colloids or nanoparticles have an average diameter which are strongly related to their composition or synthesis pathways, with a polydispersity often difficult to control.

All these advantages are clearly the direct consequence of the composition of the HPICs. Fundamentally, they are obtained by mixing a metal ion (or metal oxides, metal complexes being positively or negatively charged) and a double-hydrophilic copolymer, one block of which is able to interact with the metal ions (see Scheme 1), in a solvent. Nearly 30 types of metals have already been used as well as ca. 10 neutral and 15 ionic blocks. These various elemental bricks forming HPICs are described in the following paragraphs.



Scheme 1: Formation of hybrid polyionic complexes (HPICs) starting from double-hydrophilic block copolymers (DHBCs) and metal ions or metal complexes.

2.1 Metal ions used to build HPICs

As listed in Table 1 and illustrated in Figure 1, a large variety of metals have been used to form HPICs in solution.

Chemical Element	References
Aluminum	[44-50]
Barium	[51-56]
Cadmium	[56-59]
Calcium	[49, 51-53, 55, 60-69]
Cobalt	[54, 56, 70, 71]
Copper	[45, 49, 70-73]
Dysprosium	[74]
Europium	[75-79]
Gadolinium	[51, 75, 77-80, 180]
Gallium	[81]
Gold	[14, 82-86]
Iron	[87, 88, 152]
Lanthanum	[46, 89, 90]
Lead	[56]
Magnesium	[45, 47]
Manganese	[49, 70, 91, 92]
Molybdenum	[93]
Nickel	[56, 70, 71]
Palladium	[14, 84]
Platinum	[13, 14, 84, 91, 92, 94-129]
Rhodium	[84, 106]
Ruthenium	[130]
Silver	[131, 132]
Strontium	[52]

Thulium	[74]
Yttrium	[72, 79]
Zinc	[49, 54, 70, 133, 134]
Zirconium	[80]

Table 1: Chemical elements used for HPIC formation

Platinum and calcium have been the two most commonly used elements because of their expected applications in biology and medical science (see below). In addition to calcium, almost all alkaline earth metals have been tested. The majority of the research dealing with HPICs was based on transition metal ions, oxides or complexes in water, and some post-transition metals, such as aluminum, have been used likewise to trigger HPIC formation. Finally, one-third of the lanthanides have been studied, leading to nano-objects with similar sizes.

A large majority of the research has been based on simple multivalent metal ions with inert counterions; therefore, aqua complexes are presumably the main species interacting with the copolymers. Metal complexes have been used, possibly partially hydrolyzed. This has often been the case for platinum (used in the form of the diamino salt $[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$ issued from the cis-platine,[100, 117] 1.2-diaminocyclohexane platinum(II),[123] PtCl_6^{2-} [94] or more elaborated structures[116]), gold (mainly in the form of tetrachloroaurate AuCl_4^- [86]), palladium (PdCl_4^{2-} [14]), etc. More complex architectures, such as coordination polymers with europium, gadolinium, iron or manganese[75, 135-138] or polyoxometallates based on molybdenum[76, 93] or aluminum[44], have also been built. Finally, one should note that the development of nano-objects containing two types of metal ions has been successful by mixing metal ions in the pristine solution.[45, 49, 80, 87] Chemical stability in water and the formation of neutral oxides or hydroxo complexes may explain why some (oxophilic) metal or metalloid elements have not yet been used as building blocks for HPIC structures. In such cases, new strategies should be clearly developed in the near future: use of positively charged DHBCs like for polyoxometallates[76], of ligands interacting more strongly with the metal ions (such as phosphonate compared to carboxylate)[70, 91], of more specific complexing ligands such as diamine, bipyridine or terpyridine.[104, 139, 140] Design of DHBCs bearing such ligands should however be done in such a way the metal ions could interact and bridge more than one macromolecule in order to favor the formation of HPIC structures.

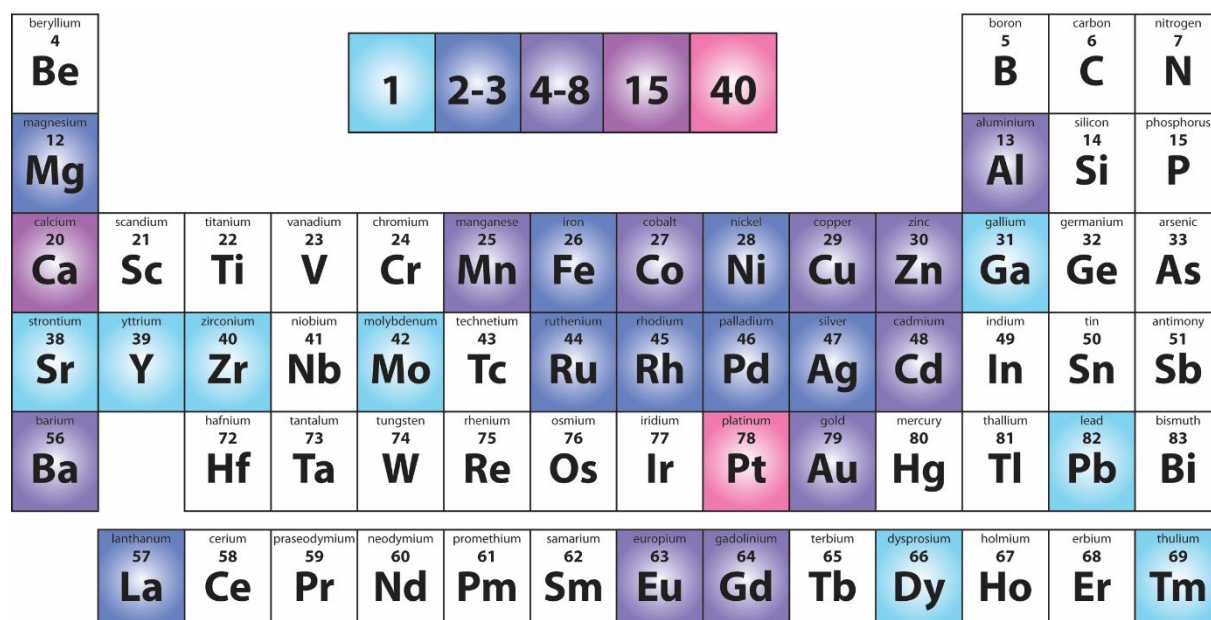


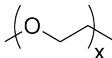
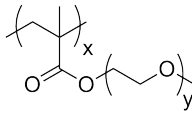
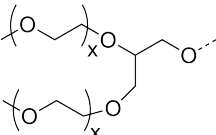
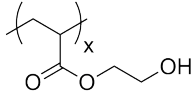
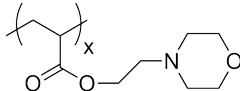
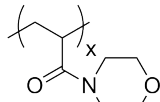
Figure 1: Number of papers describing the formation and/or characterization of HPICs built with various chemical metallic elements.

2.2 Solvent

Water is the common solvent of the metal ions and the copolymers. Therefore, water is mainly the liquid in which the HPIC structures are formed. However, some very rare papers have described similar colloids built in organic solvents. A. Eisenberg formed micelles in toluene with poly(styrene)-*block*-poly(acrylic acid) associated with nickel, cobalt or barium ions.[56] L. Zhang organized polyoxometalate into hybrid micelles based on poly(styrene)-*block*-4-poly(vinylpyridine) dispersed in chloroform.[93] In both examples, hydrophobic poly(styrene) acted as the neutral block of the copolymer when either aromatic amine or carboxylic groups linked to the second block interacted with the metal ions. In this review, we will focus our attention on the HPICs obtained in water.

2.3 Polymers used to build HPICs

The archetypical structure of the polymers leading to HPIC structures is a double-hydrophilic copolymer made of a neutral block and a block that is able to interact with metal ions. Table 2 describes the various chemical structures of the neutral blocks. In the literature, an overwhelming majority of polymeric systems are based on poly(ethylene oxide) either as a simple linear block (PEO) or grafted on a small block such as poly(methacrylate) (see the example of PEGMA). Few references report on systems based on poly(acrylamide) or its derivatives (including the thermosensitive and well-known PNIPAM). Polymeric blocks bearing hydroxyl or morphine functional groups (see PHEA, PMEMA, and PNAM) have also been used with success. A couple of papers have described experiments performed with the interesting poly(2-alkyl-2-oxazoline). On average, the molar mass of the block is approximately 10 kg.mol⁻¹, with a minimum value of 2 kg.mol⁻¹ and a maximum of approximately 60 kg.mol⁻¹. In terms of the degree of polymerization, the lowest value of 4 corresponds to a small oligomer, and the maximum is approximately 800.

Neutral polymer block: abbreviations, structures and names		References
PEO Poly(ethylene oxide)		Large majority of the references
PEGMA Poly(oligoethylene glycol methacrylate) y ~ 6		[69, 94-96, 100, 101, 104, 110, 115]
2 armed PEO Poly(ethylene oxide)		[122]
PHEA Poly(2-hydroxyethylacrylate)		[44, 46, 48, 50]
PMEMA Poly(2-(N-morpholino)ethyl methacrylate)		[65]
PNAM Poly(N-acryloylmorpholine)		[49]

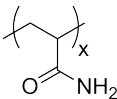
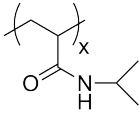
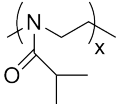
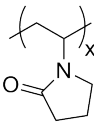
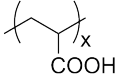
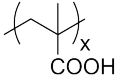
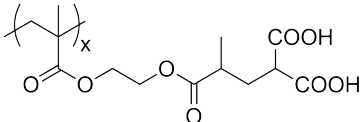
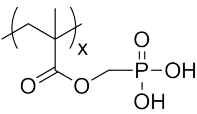
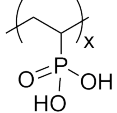
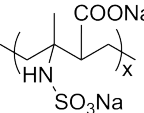
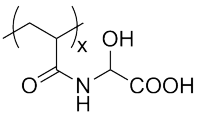
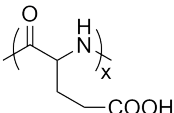
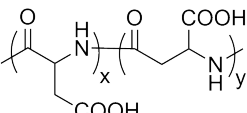
PAM Poly(acrylamide)		[46-48, 70, 89, 90, 134]
PNIPAM Poly(N-isopropylacrylamide)		[67]
PiPrOx Poly(2-isopropyl-2-oxazoline)		[58, 71]
PVP Poly(N-vinyl-2-pyrrolidone)		[79]

Table 2: Examples of neutral polymer blocks used to form HPICs

Metal interacting polymer block: abbreviations, structures and names		References
PAA Poly(acrylic acid)		[44, 46-48, 50, 51, 57, 61, 70, 73, 78-81, 85, 86, 89, 90, 92, 98, 100, 109, 115, 116, 134]
PMA Poly(methacrylic acid)		[51, 53, 55, 62-64, 67-69, 110, 131]
PMAETC Poly(3-(2-(methacryloyloxy)ethyl) butane-1,1,3-tricarboxylate))		[101]
PMOMP Poly((methacryloyloxy)methyl phosphonic acid)		[65]
PVPA Poly(vinyl phosphonic acid)		[152, 180]
PSCI Poly(sodium(sulfamate carboxylate))		[59]
PAGA Poly(2-acrylamido glycolic acid)		[49, 58, 71]
P(Glu) Poly(glutamic acid)		[97, 103, 105, 107, 117, 119-124, 126, 128]
P(Asp) Poly(aspartic acid)		[13, 99, 112-114]

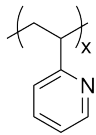
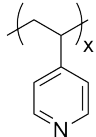
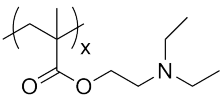
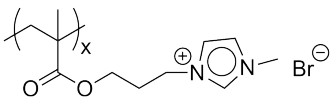
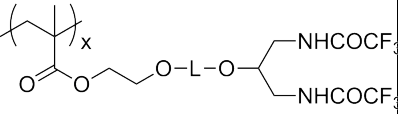
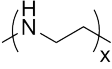
P2VP Poly(2-vinylpyridine)		[84, 96, 108]
P4VP Poly(4-vinylpyridine)		[77, 127, 133]
PDEAEMA Poly(2-(diethylamino)ethyl methacrylate)		[72, 76, 94-96]
PMMPIm Poly(1-methyl-3-(2-methacryloyloxypropyl)imidazolium bromine)		[83]
Modified PHEMA Modified Poly(hydroxyethyl methacrylate) (L is a linking group)		[104]
PEI Poly(ethylene imine)		[14, 106]

Table 3: Examples of metal interacting polymer blocks used to form HPICs

For the polymeric block that interacts with the metal ions (through ionic, ionic-covalent or donor-acceptor interactions, for example), two types of polymers have been used: one based on carboxylic or other functional groups that can be negatively ionized, and the second based on amine functional groups that easily interact with the metallic species through their free electron doublet on the nitrogen atom. In the following part of this review, we will often refer to this polymeric block simply but although inaccurately as an “ionic block” or “metal interacting block”. It should be emphasized that HPIC formation is not simply due to ionic interactions, as in polyelectrolytes and coacervates. Indeed, a metal cation can interact with both anionic block copolymers (such as poly(acrylic acid)) and potentially cationic block copolymers (such as poly(vinylpyridine)).

The two different polymeric blocks could form different complexes with the metal ions, in which the ionic interactions may or may not be important. This complexation strength is clearly paramount, even if the correlation between complexation and HPIC stability has yet to be demonstrated experimentally. Table 3 lists the different chemical structures of this metal-interacting block for building HPICs. Poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMA) have been largely described in the literature as polymeric blocks for obtaining HPICs. Indeed, complexation between carboxylic groups and metal ions is well known and relatively universal.[141-143] The free carboxylic groups of poly(amino acid) (such as poly(glutamic acid (P(Glu))) or poly(aspartic acid) (P(Asp))) have been used to form HPICs. In addition to carboxylic acid, phosphonic acid is an interesting pendant group, as in PMOMP. Indeed, interactions between phosphonic acid and metal ions are often stronger and less pH-sensitive.[144, 145] Concerning the second group of polymers containing amine functional groups, poly(vinylpyridine) (P2VP or P4VP) and alkyl amines, such as PDEAEMA or PEI, have been used. Such systems have been less analyzed than those based on negatively charged functional groups.

On average, the molar mass of the “ionic” block is approximately $5 \text{ kg}\cdot\text{mol}^{-1}$, with a minimum value of $0.7 \text{ kg}\cdot\text{mol}^{-1}$ and a maximum of approximately $41 \text{ kg}\cdot\text{mol}^{-1}$. In terms of the degree of polymerization, the lowest value is approximately 11, and the maximum is approximately 470. Thus, the ionizable block is often smaller than the neutral block. Presumably, an ionic block that is too small could limit the number of metal ions interacting with different macromolecules and stabilizing the HPIC structure by cross-linking due to metal-polymer interactions. Ionic blocks that are too large seem to have the tendency to lead to poorly defined self-aggregation with limited size control.

Before focusing this review only on the previous double-hydrophilic copolymers, one should note that other polymeric structures have been proposed for building HPICs. A simple example is the functionalization of one end of a DHBC by pyrene, cholesterol or boronic groups, which can affect the properties of the final nano-objects.[92, 100, 122, 124] Grafted structures containing neutral groups and “ionic” groups have also been suggested,[54, 91, 146-148] as well as copolymers bearing chemical ligands designed to efficiently form metal complexes.[77, 104, 149, 150] Finally, triblock structures with a hydrophobic block for inducing or facilitating self-aggregation are also discussed.[151]

3. HPIC formation

Because HPIC formation involves mixing water-soluble species, the experimental protocols are often simple. Metal ions with various counterions have been simply dissolved in water. For some systems, the metal complex has been chemically modified before adding the copolymer. For instance, cis-dichlorodiaminoplatinum(II) (or CDDP) was mixed with two equivalents of AgNO₃ to obtain cis-diaminediaqua platinum(II).[105] After adding a polymer solution, the mixture was incubated at room temperature for a few minutes and up to 2-3 days depending on the chemical systems. The resulting solution was used without purification, after centrifugal filtering or dialysis with a membrane of low molecular cutoff (to eliminate free metal ions). The metal content in the solutions could be titrated by inductively coupled plasma–mass spectrometry (ICP–MS) or other more specific techniques. During this process, the pH can be adjusted to ionize the chelating polymeric functional groups and/or to avoid the dismutation or hydrolysis of aqua metal complexes.

Regardless of the mixture process, the main parameter controlling the final result is always the ratio between the metal ion concentration and the number of metal chelating functional groups in the dissolved polymer. This is often expressed as a ratio, denoted here as Z, between the charges brought by the metal ions (Mⁿ⁺) and the (maximum) charges due to the polymers:

$$Z = \frac{n \cdot [M^{n+}]}{\alpha \cdot Dp_i \cdot [Polymer]}$$

where α is the charge of one functional group interacting with the metal ions (for example, 1 for the carboxylate group) and Dp_i is the degree of polymerization of the ionic block of the polymer.

Electroneutrality between the polymer and the metal ions is therefore expected for $Z = 1$.

HPIC formation in solution by ion addition (or, in other words, titration of the polymer by the metal ions) can be easily monitored by measuring the chemical-physical properties of the objects in the solution versus this Z ratio. Figure 2 shows a typical example with zeta potential measurements for various Z ratios in Ca²⁺/PEO-b-PMA.

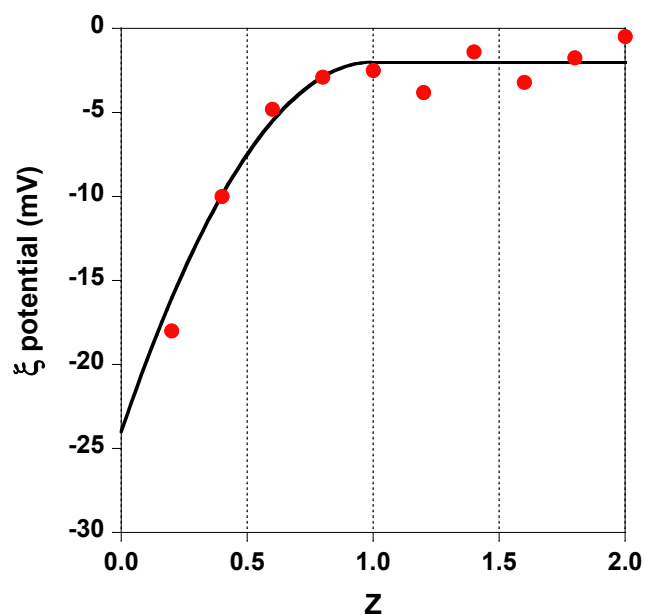


Figure 2: Evolution of the zeta potential for a solution of PEO-b-PMA with various amounts of calcium ions expressed in terms of the Z ratio (see text). Adapted from reference [64].

The initial potential of the polymer in solution was strongly negative (for negatively charged block copolymers) and increased when the metal ions were added. It became constant after complete HPIC formation, therefore for a Z ratio above unity. Regarding this plateau, adding metal ions increased the quantity of free metal ions in the solution but did not modify the HPIC properties. Such evolution of the zeta potential (or the electrophoretic mobility) versus the addition of ions to a copolymer solution has been observed for different systems.[64, 73, 78, 89, 115] The titration of free metal ions in the solution corroborated the previous interpretation: no free ions were detectable for Z lower than ca. 1, a critical value above which the concentration of free metal ions in the solution increased linearly.[63] NMR experiments have also been performed to follow the aggregation linked to metal ions.[13, 81, 83, 94] For instance, for PEO-PMMIIm copolymers in the presence of AuCl_4^- , [83] the liquid ^1H NMR signals associated with the imidazolium groups interacting with the metal ions disappeared when Z increased. This suggests that the mobility of such groups diminished in the presence of gold ions. In contrast, the signals associated with the PEO group were more or less constant, showing that the mobility of these neutral blocks was maintained during HPIC formation. Similar behavior was observed for PEO-PAA copolymers when interacting with gallium. More precisely, the longitudinal relaxation time (T_1) of the protons in β of the carboxylate units was constant when the Z ratio was below 0.75 and then rapidly increased to reach a plateau above $Z = 1$. This evolution demonstrated that HPIC formation occurred with restricted motion of polymer chains for Z above 0.75. Below this value, no aggregation was evidenced, and the polymer roughly behaved as isolated or poorly associated chains. Such a result suggested that the aggregation was not a “linear” process occurring continuously. Interestingly, in this system, NMR could also be used to monitor the metal ions and their interactions with the polymers by ^{71}Ga or ^{195}Pt NMR.[81, 101, 129] Generally, IR spectroscopy is used to characterize the complex formed between the metal ions and the interacting functions of the copolymers.[54, 86, 89, 93, 109, 130, 150, 152]

Metal/polymer aggregation has been indirectly analyzed by previous techniques. To demonstrate the formation of colloids containing a large number of copolymers, scattering techniques should be used. Among all these methods, dynamic light scattering (DLS), possibly associated with static light scattering (SLS), was used in almost all the studies reported in the literature. Unfortunately, the analysis of DLS data can be somewhat tricky, and many authors do not properly describe the mathematical method used and the type of hydrodynamic diameter (average in number, in volume or in intensity) that they report, limiting comparisons between various scientific studies.

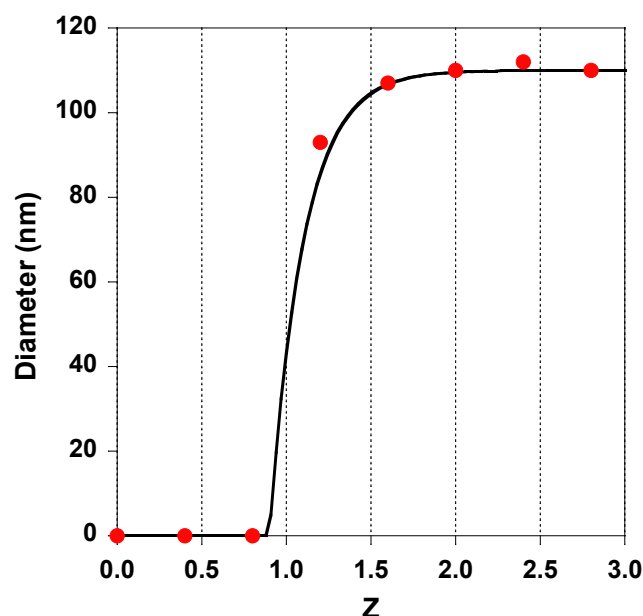


Figure 3: Evolution of the diameter of the aggregates (estimated by DLS) for a solution of PEO-b-PMA (0.5 g. L⁻¹) with various amounts of barium ions expressed in terms of the Z ratio (see text). Adapted from reference [53].

For instance, Figure 3 shows the mean diameter of the colloids inside a solution of PEO-b-PMA mixed with barium ions. Initially, this diameter increased with Z and then reached a plateau. This behavior has been described for a large majority of metal/copolymer systems. In SLS, the standard behavior is an increase in the scattering intensity reaching a plateau.[61] This explains why turbidity is also a popular technique used to monitor polymer aggregation.[51, 55, 68]

Small angle X-ray scattering (SAXS) is also a powerful technique for demonstrating the formation of polymeric aggregates.[52] The Ga/PEO-PAA system was used to show that HPIC formation occurred mainly above a Z ratio of 0.7-0.8, as seen by NMR.[81] SAXS and SANS (small angle neutron scattering) are highly useful for more deeply investigating HPIC formation and architecture, as discussed below.

Very rare data concerning HPIC formation kinetics are available. For platinum, a few hours were needed to reach some kind of equilibrium[100], whereas the average kinetic constant of aggregation was close to 0.2 s in a system based on gallium[81], suggesting that a few minutes was enough to reach equilibrium. The formation kinetics should be strongly dependent on the metal/copolymer nature and deserve more characterization in the future.

Table 4 briefly describes the advantages and drawbacks of the main techniques used to characterize the formation of the HPIC in solution.

Technique	Indirect or direct characterization of the HPIC formation ^(a)	Advantage	Drawback
Zeta potential	Indirect	<ul style="list-style-type: none"> Fast and easy to perform Easy to titrate the polymer by the metal ions (or reverse) 	<ul style="list-style-type: none"> Possible chemical reaction of metal ions with electrodes in the zeta potential cell Buffer or complex medium may interfere with the measurements

			<ul style="list-style-type: none"> • Often no quantitative interpretation
UV-visible or fluorescence	Indirect	<ul style="list-style-type: none"> • Highly available • Fast and easy to perform • Easy to titrate the polymer by the metal ions (or reverse) • Provides information on the coordination sphere of the metal ions • May be used to estimate equilibrium constant • May be used to follow the metal ions exchange 	<ul style="list-style-type: none"> • Not general to all metal ions • Polymer absorption (emission) may mask the absorption (emission) due to the metal ions
FT-IR	Indirect	<ul style="list-style-type: none"> • Highly available • Fast and easy to perform • Provides information on the coordination sphere of the metal ions 	<ul style="list-style-type: none"> • Usual processes imply drying the HPIC solution, possibly resulting in changes in the organization • The ligands interacting with the metal ions should present well defined and easy to attributed bands
NMR	Indirect	<ul style="list-style-type: none"> • Highly available • Probes at the molecular level the polymer and some metal ions. 	<ul style="list-style-type: none"> • Not possible with all metal ions • All the possibilities and technics of NMR have not been applied to the HPIC study yet
ITC	Indirect	<ul style="list-style-type: none"> • Quantitative characterizations of the metal/polymer interactions 	<ul style="list-style-type: none"> • Depending on technical specificities of the used apparatus, some metal or polymer could not be recommended for ITC measurements. • Need to choose a model for data interpretation
Dynamic light scattering	Direct	<ul style="list-style-type: none"> • Universal method • Fast and easy to perform • Combined with SLS, may provide structural information 	<ul style="list-style-type: none"> • Tricky interpretation of the data when the population is not monomodal • Qualitative interpretation for non-spherical objects
SAXS	Direct	<ul style="list-style-type: none"> • Lead to precise structural data • ASAXS may lead to data concerning the metal ions 	<ul style="list-style-type: none"> • Often need a synchrotron facility • Need to choose a model for data interpretation
SANS	Direct	<ul style="list-style-type: none"> • Gives precise structural data • Specific deuteration may provide precise information on the blocks of the copolymer 	<ul style="list-style-type: none"> • Need of a nuclear facility for SANS measurements • Need to choose a model for data interpretation

Within this difficulty in mind, no correlation between the HPIC diameter and the type of metal ions is detected from such a figure. Analysis of the literature data also does not indicate a relationship between the HPIC size and the chemical nature of the polymers used. However, extracting data, such as the length of the polymers (in terms of the degree of polymerization of the two blocks), charge of the metal ions, HPIC size, etc., allows one to calculate a covariance matrix between these parameters (see Figure S1). Again, no correlation is found between the charge of the metal ions and the hydrodynamic diameter: the covariance between these two parameters is close to zero. However, a slight (positive) correlation (covariance values of approximately 0.3-0.4) exists between the length of the two blocks of the copolymers or the total length of the polymer expressed in terms of the degree of polymerization and the HPIC size. Such a correlation has already been studied for specific metal ion/copolymer systems. For example, N. Sanson et al. demonstrated that the hydrodynamic diameter of HPICs made of PAA-b-PAM copolymers increased as a power law of the total mass of the polymer. The experimental power exponent was approximately 0.6-0.7 depending on the type of metal ion (Al^{3+} , La^{3+} or Al_{13}^{7+}).[46] PiPrOx-b-PAGA mixed with cadmium also showed a clear increase in the mean diameter from 160 to 320 nm when the polymer length increased by 50%.[71] Of course, if one block was constant, an increase in the second block length generally led to a larger object. For instance, the Pt/POEGMEMA₅₀-b-PMAETC_x system exhibited a diameter ranging from 77 nm to 176 nm for an x equal to 27 and 80, respectively.[101] In contrast, data in the literature also suggest that an ionic block that is too short will not induce HPIC formation because of insufficient entropy gain.[70]

As shown in Figure 5, with the exception of four elements (Rh, Pd, Co and Ba), the minimum HPIC size is always below 30 nm in diameter, with an average value of approximately 20 nm. Such a size is therefore typical for HPICs. Concerning HPICs with Rh, Pd and Co, too little experimental data are available to draw conclusions about the specific behavior of the corresponding HPIC systems. For Ba, as well as for all alkaline earth metals (Ca, Mg), the interactions with the copolymers bearing carboxylic groups may be too weak to lead to dense and well-defined HPICs. This was noted by C. Gérardin and coll. for Mg.[47] For Ca, the data indeed suggest that the polymer was not fully neutralized at Z=1 by the metal ions and/or that aggregation occurred only for higher Z.[67, 68]

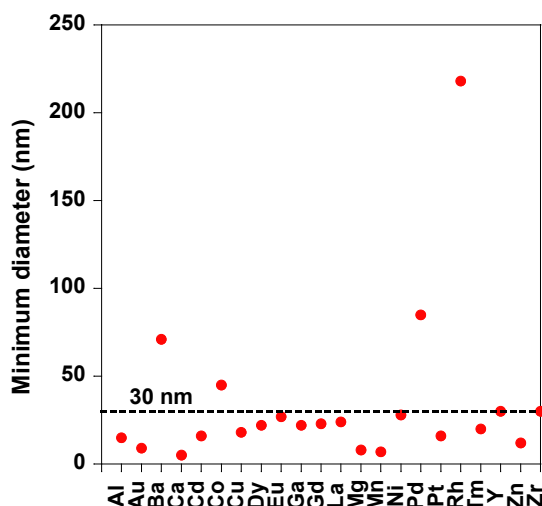


Figure 5: Minimum value of the hydrodynamic diameter of HPICs measured by DLS reported in the literature versus the chemical nature of the metal element.

Interestingly, K. Kataoka and coll. demonstrated that the average diameter of HPICs can be adjusted by adding the ionic block homopolymer to the metal/copolymer mixture. Indeed, the HPICs of Pt/PEO-b-P(Asp) had a diameter of approximately 20 nm. When the authors added P(Asp) homopolymer, they recorded an increase

in the average size of the HPICs. For a ratio of $[P(\text{Asp})]/[PEO\text{-}b\text{-}P(\text{Asp})]$ equal to three, the mean diameter was found to be approximately 100 nm.[112]

4.2 Shape and internal structure of the HPICs

HPICs are described as isotropic spheres in an overwhelming amount of cases. For the smallest size, a core-shell structure has been clearly demonstrated. Such a structure was suggested by simple zeta potential measurements, which were close to zero and generally slightly negative for HPICs (the average value on all data available for all types of metal ions and polymers is -6 ± 3 mV). This suggests that the neutral block of the copolymer should form a (neutral) shell around the ionic core of HPICs. Transmission electron microscopy (TEM) is also in favor of such architecture. The cores of the particles in which the heavy metal ions should be localized are more or less diffuse in TEM images and have a size (as expected) smaller than the hydrodynamic diameter of the HPICs.[89, 96, 117] Rarely, the core-shell structure can be seen (or glimpsed) directly or after staining.[48, 103] Other microscopic techniques, such as atomic force microscopy (AFM), enable the characterization of HPICs deposited onto solid surfaces.[72, 127, 128]

However, definitive proof of this architecture in solution is given by SAXS[52, 81, 117] or SANS.[44, 46, 50, 52, 90] As seen in Figure 6, large differences between simple copolymer and HPIC solutions were recorded in SANS curves.[44] The large- q range of the HPIC curve demonstrated that the nano-objects have a diffuse shell made of polymer blocks in a good solvent, and the sharp decrease in the scattered intensity of the lower q -range suggested a sharp interface between this shell and a dense core. SAXS experiments suggested a similar model of HPIC architecture. Interestingly, SAXS also led to insights concerning the structuration as bundles of α -helices in the core of micelles made of the polypeptide P(Glu).[117] Finally, a few things are noteworthy concerning ASAXS (Anomalous Small Angle X-ray Scattering). If ASAXS was used to characterize metal nanoparticles embedded in a copolymer,[127] this technique would also be interesting to use for obtaining structural information concerning the localization of specific ions within HPICs.[81] It was used to demonstrate, for instance, that gallium ions were concentrated in a volume equivalent to that of the chelating block (PAA in the copolymer PEO-PAA) and lost this particular organization when the HPICs were de-structured or below the threshold value of Z .

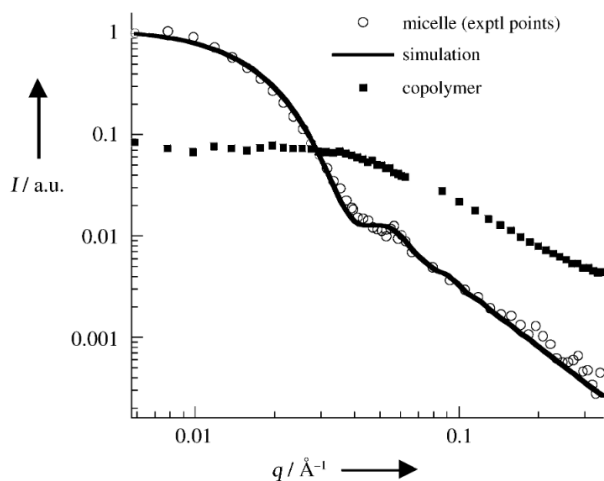


Figure 6: SANS curves of HPICs made of copolymer PHEA-*b*-PAA and Al_{13}^{7+} ions in D_2O . Reprinted with permission from reference [44]. Copyright 2003 Wiley.

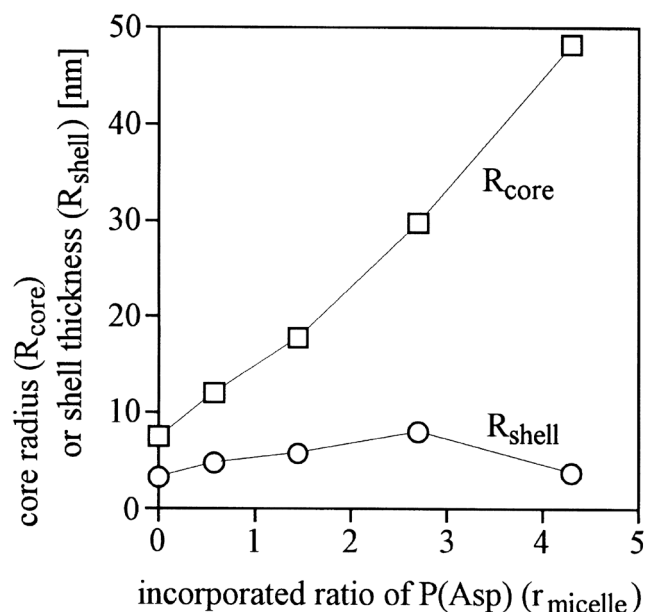


Figure 7: Change in the core radius and shell thickness for PEO-b-poly(Asp)/poly(Asp) mixtures with Pt versus the ratio, denoted as $r_{micelle}$, between homopolymer poly(Asp) and diblock PEO-b-poly(Asp). Reprinted with permission from reference [112]. Copyright 2001 Elsevier.

Unfortunately, all these careful characterizations of HPICs in solution were performed only on small assemblies (i.e., below 20-30 nm in diameter). All larger structures were mainly analyzed through light scattering and microscopy; their inner organization is still unknown and cannot be considered a “simple” core-shell structure.

For regular HPIC micelles, scattering techniques allow one to obtain information concerning the inner structures as well as the number of aggregations, i.e., the number of copolymers assembled to form a single HPIC. The size of the HPIC core is slightly positively correlated with the hydrodynamic diameter, but no meaningful correlation is found between the length of the various polymeric blocks and the core diameter (see Figure S1). The core sizes determined by SAXS or SANS are in the range of 9 to 37 nm, which is also the typical range of the core diameter one can estimate through TEM experiments (found to be between 5 and 40 nm). The only way to modify in a controlled fashion the size of the core appears to be the mixing of copolymers with homopolymers described above. Indeed, as shown in Figure 7, the HPICs made of this mixture of polymers have a somewhat constant shell thickness (due to the copolymers), and the size of the core was the only geometrical parameter that was modified with the addition of the homopolymer.

This HPICs core size was often used to estimate the mean number of polymers within each HPIC micelle, i.e., the aggregation number. Starting from the core diameter D_c determined by TEM or SAXS and assuming that the micellar core has more or less the same density as a reference compound (often just the homopolymer having the same nature as the ionic block of the DHBC), [81, 92, 115] the aggregation number (N_{agg}) was roughly estimated through the following relationship:

$$N_{agg} = \frac{\pi}{6} \cdot D_c^3 / (V_i \cdot D_{pi})$$

where V_i is an estimation of the molecular volume of one unit of the ionic block having a degree of polymerization D_{pi} .

This aggregation number may also be directly determined by fitting the SAXS or SANS curve with a model in which N_{agg} is an adjustable parameter. [46, 52] Calculating the number of metal ions within an HPIC using models fitting ASAXS curves also leads to an estimation of the polymeric aggregation number assuming electroneutrality in the core. [81]

SLS experiments (or other techniques) have led to an approximation of the molar mass of the HPIC micelles. This mass was divided by the molar mass of the copolymer or by the mean molar mass of the copolymer and the metal ions to obtain the aggregation number. [59, 112, 117, 133]

Experimentally, the aggregation number was found to be between 7 and 390 (with a mean value of approximately 110) copolymers per HPIC micelle. In terms of metal ions, the number of calcium or barium ions trapped in the micelles has been estimated to be between 40000 and 86000. For the other metals, an average of 3100 metal ions was estimated within the HPIC cores (minimum value 12, maximum value 11700). Finally, analysis of the literature suggests a clear and negative correlation between the charge of the metal ions and the aggregation number (see Figure S1). Such a hypothetical relationship merits full analysis in the near future.

All the previous HPICs were described as isotropic spherical objects. However, a few rare cases of more complex structures can be found in the literature. Whereas an isotropic core-shell structure was found for the Pt/PEGMA-b-PAA systems, attaching a mesogenic cholesterol moiety to the end of the PAA block led to changes in the aggregate morphology: the HPIC center appeared to have a lower metal density, presumably because of the presence of the cholesterol groups.[100] This is close to a kind of core-double shell structure. G. Qiao et al.[118] showed that PEO-b-P(Glu) copolymers with platinum can form vesicular structures with an external diameter of approximately 300 nm. The authors suggested that a large neutral block and a short ionic block (with a molar ratio between them of approximately 10%) explain the formation of vesicles instead of micelles generally observed for such copolymers and metal ions. A few years before, K. Kataoka and coll.[122] also obtained similar vesicles (called metallosomes) using two-armed PEO linked to P(Glu) mixed with platinum. They found an average membrane thickness of ca. 6 nm for a total vesicle diameter of approximately 100 nm. Systems based on reversible coordination polymer (a cationic DHBC) using Zn^{2+} , Mn^{2+} , Co^{2+} or Ni^{2+} and a small anionic molecules have been more recently described as mixtures forming vesicles with a radius of ca 50-80 nm.[153]

Block PEO-b-PAA copolymers mixed with platinum exhibited a large panel of structures depending on the size of the PAA block and the quantity of metal ions.[109] In addition to the regular core-shell structure obtained for small PAA blocks, crew-cut spheres as well as partially fused spheres were observed for larger PAA blocks (see Figure 8). When the Pt content increased, these fused spheres led to bilayers and vesicles. The fusion appeared to be driven by interactions between the platinum and the PEO groups, and interactions occurred when Z was higher than one.

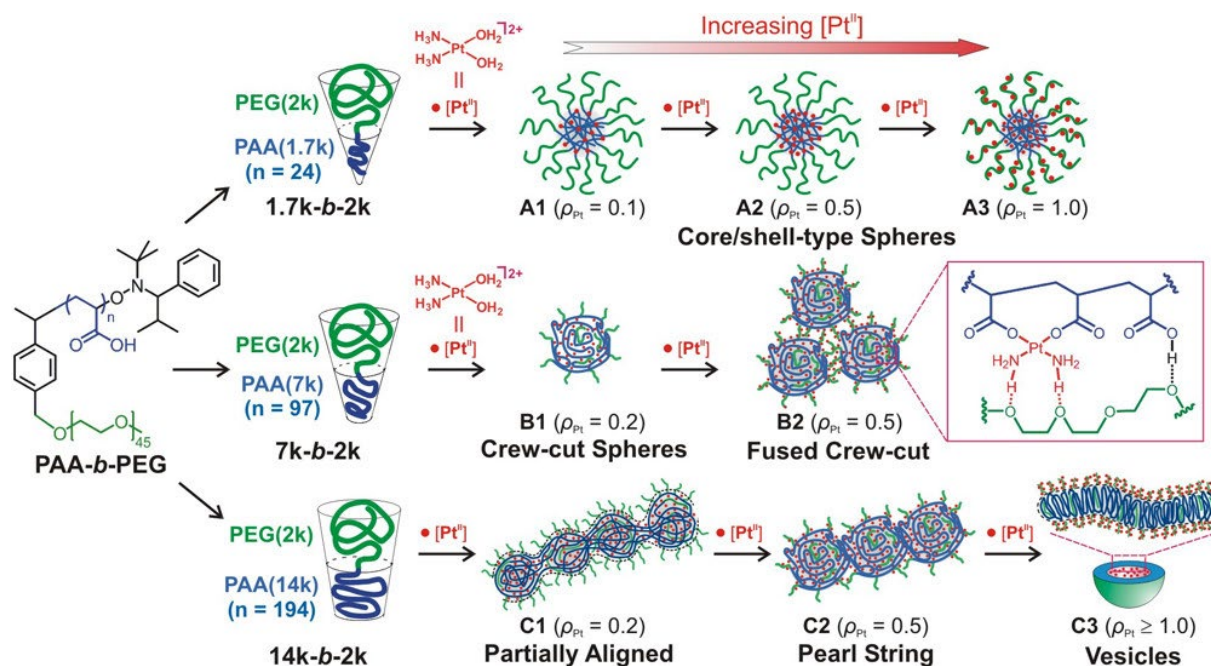


Figure 8: Various morphologies of Pt/PEO-b-PAA HPICs depending on the length of the chelating block and the Pt expressed in terms of $\rho = Z/2$. Reprinted with permission from reference [109]. Copyright 2020 American Chemical Society.

Similar changes from spherical to elongated structures were described by F.H. Schacher and coll. for PNAM-b-PAGA copolymers with calcium or copper ions and Z values larger than 1.[49] Recently, the same authors found an interesting system for which the final aggregate structures can be adjusted, by not only the Z ratio but also

the nature of the metal ions. Indeed, with the PiPrOx-b-PAGA copolymer, adding cobalt mainly led to spherical micelles, whereas the addition of nickel ions led to a worm-like structure.[71]

4.3 Metal surrounding within the HPICs

SAXS and SANS techniques are powerful tools for determining HPIC size and structure. However, very few data are obtained concerning the molecular organization at the level of the metal centers. Indeed, the exact type of metal complexes (number and nature of the ligands, symmetry, etc.) within HPICs are usually not characterized.

Isothermal titration calorimetry (ITC) has been reported for HPICs built from calcium ions in three papers and in one from barium and strontium.[49, 52, 61] For these three types of metal cations, the experiments suggested that the binding between the cations and the polymers is driven by entropy.[52] The enthalpy and the entropy of binding decrease in the order $\text{Ca}^{2+} > \text{Sr}^{2+} > \text{Ba}^{2+}$. This evolution should be related to the amount of water released from hydration shells upon binding. To our knowledge, no other report has been made concerning studies of metal/copolymer interactions by ITC. The binding affinity of metal-ligand in the HPICs is therefore generally unknown even if such experiments were already performed in bulk material.[140, 154] Various authors reported FT-IR experiments which demonstrated the interactions between the metal cations and the complexing functions of the polymers.[54, 109, 118] When these complexing functions are carboxylic groups, the shift between the CO asymmetric and symmetric stretching modes is related to the type of coordination (ionic, monodentate, bidentate, bridging).[155] A monodentate coordination mode with gadolinium ions and PAA was therefore suggested[79], a bidentate mode for La^{3+} and PAA[89] and a bridging mode between gold ions and carboxylate groups.[86] No more precise information concerning the coordination number of the metal ions has been extracted from such FT-IR data. UV-vis absorption or fluorescence were also used to demonstrate the interactions metal ion/polymer interactions.[72, 73, 77, 79, 99] In the particular case of europium ions, measurements of europium lifetime in H_2O and D_2O provided an estimation of the number of bound water molecules.[79, 80] This data lead to a hypothetical coordination sphere close to $\text{Eu}(\text{COO})_3(\text{H}_2\text{O})_4$. Emission spectra of europium in polyoxometalate showed a lower symmetry of europium within the HPICs, suggesting the release of water molecules during the hybrid micelle formation.[76] NMR was also sparkly used to probe the complexation of the metal ions by the polymers. As mentioned above, ^1H NMR experiments are often just analyzed to demonstrate the stiffening of the ionic polymeric block (presumably due to interactions with the metal ions).[13, 55, 62, 79, 81, 109] ^1H NMR was used to estimate the mean number of acetate functional groups around gold ions.[85] Very rarely, NMR was used to probe the metal ions directly. ^{71}Ga NMR showed, for example, that the highly symmetrical surroundings of hydrated gallium was lost during the HPIC formation, suggesting that the coordination sphere has a much lower symmetry in the HPIC core.[81] In ^{27}Al NMR experiments, the characteristic peak of the tetrahedral site in Al_{13} clusters vanished when the clusters are trapped within the HPIC core.[44] ^{195}Pt NMR demonstrated, as expected, that the diamino ligands of the selected polymer are conjugated with the platinum ions, but that oxygen was also possibly involved as a ligand.[104] In the case of a polymer bearing dicarboxylic functions, ^{195}Pt NMR proved that the main Pt complexes involved the two carboxylic functions but that a small fraction of complexes is based on a monocarboxylate ligand.[101]

The previous paragraph illustrates the lack of characterization of the coordination sphere of the metal ions within the HPIC structures. To precisely and experimentally determine the geometrical environment of the metal ions within the HPICs, two main difficulties are encountered:

- 1) All the metal ions do not have the same exact environment. The number of complexing functions, the number of bound water molecules, the geometry of the metal complexes... may vary inside the core the HPICs. Furthermore, the lability of the complexes and of the HPICs structure may introduce dynamic equilibria which should make structural analysis more complicated.
- 2) The HPICs exist in water and they are amorphous material. Therefore many techniques of characterization cannot be used in the HPICs solutions and, in particular, X-ray diffraction is useless (see for example [128]).

These difficulties combined to the fact that the researchers dealing with HPICs are often polymer chemists, physical-chemists or biologists but not specialists of metal complexes have clearly limited the precise determination of the metal coordination sphere within the hybrid micelles. One way to resolve this in the near future is to apply, to the HPIC systems, the technics and strategies used to elucidate metal ion/biomolecules (DNA, peptides, proteins...) interactions.[156, 157] Combining ITC,[158] electronic absorption, EPR[159], fluorescence, FTIR, NMR, even mass spectroscopy[160] will provide a more precise picture of the metal

surrounding (including coordination numbers) within the HPIC architecture. The study of the metal coordination sphere and its variability within the HPICs is clearly a challenging subject for future work.

5. Stability of the HPIC structures

HPICs have a high colloidal stability due to the steric hindrance stabilization induced by the neutral block forming the outside shell: various authors have reported stability for several weeks.[50, 99] In fact, the addition of a high concentration of sodium chloride has no effect on colloidal stability,[44] but it may lead to the leakage of metal ions due to the formation of chloro complexes.[99] Such an external shell may also explain the stability under freeze-drying conditions.[46, 115] Diluting pristine HPIC solutions does not induce the expected instantaneous aggregate dissociation.[49, 78] One may therefore hypothesize that HPICs are not necessarily at the thermodynamic equilibrium but are kinetically trapped. Unfortunately, no deep study of this point has been conducted thus far, even if ITC experiments have been performed to attempt to estimate the thermodynamic data of such metal ion/copolymer interactions.[49, 61] Various authors have also measured critical micelle concentration or aggregation,[72, 100, 115, 121, 125] even if the nature (frozen or dynamic) of the HPICs are unknown. Indeed, as pointed out for copolymer aggregates and contrary to micelles made of small surfactants, exchange of polymers between the solution and aggregates can be very slow. The polymeric chains can be considered as kinetically trapped inside the aggregates. For some specific experimental conditions and/or chemical composition of the copolymer, fast exchange may exist leading to a thermodynamic equilibrium of the copolymer micelles with the solution.[161] Even if no experimental data are available, this kinetic of exchange should presumably depend on the type of metal ions, the strength of their interactions with the complexing functions of the copolymers as well as the lability of such functions when interacting with the metal center. Ligand exchange dynamics highly depend on the nature of the metal, its oxidation state and its inner sphere of coordination.[162-164] Theoretical models are clearly missing for obtaining a full comprehensive picture of these metal ion/copolymer systems, and no strong effort has been made to connect experimental data with some models available in the literature.[165-167]

The weakness of HPIC structures is their low stability versus pH. Indeed, for a negatively charged ionic block, a decrease in pH should induce the neutralization of the complexing groups and therefore the release of the metal ions and the loss of the HPIC architecture. For example, the carboxylic group in the PAA block should have an acid dissociation constant (noted K_a^0) with pK_a^0 of approximately 4.3-4.5.[168, 169] A release of metal ions was often detected at approximately 4 (see Figure 9) with a concomitant loss of the micelle structure, as shown, for example, by DLS.[69]

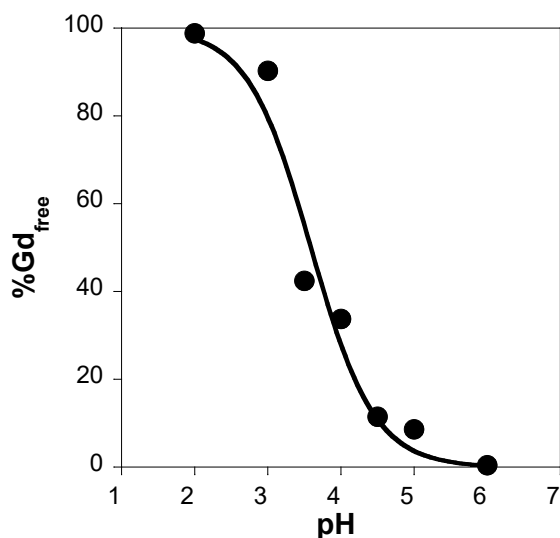


Figure 9: Percentage of free gadolinium ions at various pH values compared to the initial quantity of gadolinium trapped within Gd/PEO-b-PAA HPIC at pH 6. Reprinted with permission from reference [109]. Copyright 2016 American Chemical Society.

However, the deaggregation due to pH occurs with a shift compared to the previous value of the pK_a^0 . The apparent pK_a should indeed be taken into account, and the difference between the apparent pK_a and the pK_a^0 is related to the strength of the metal ion/polymer interactions. For instance, a shift of ca. 1, 3 or below 4 units were found for Gd^{3+}/PAA [109], Ga^{3+}/PAA [81] and ZrO^{2+}/PAA , respectively.[80] The nature of polymeric complexing groups will of course strongly influence this stability versus pH (phosphonate groups should lead to more stable structures, for example). Furthermore, high pH could also limit HPIC strength since hydroxides can interact with metal ions, leading to metal-hydroxo complexes. The pH can be lowered to induce a faster release of metal ions[115] or to check the reversibility of HPIC formation/destruction versus pH.[49]

To avoid HPIC deaggregation, cross-linking of the copolymer has been proposed. The reaction between amine and glutaraldehyde[150] or ethylene diamine and EDC,[51, 62, 66, 68, 102] froze the structure, which appeared to be more stable even under high dilution conditions. Such frozen structures did not mean that the metal ions were irreversibly trapped in the HPICs. Indeed, in some of the previous examples, calcium was used to organize the copolymers before cross-linking and was eliminated in a second step. Furthermore, other metal ions can also be in competition for the complexing sites inside HPICs: the exchange of ions from the solution into the HPICs has been studied. Calcium was too weak to replace copper or manganese in HPICs[49, 91], but copper displaced gadolinium, etc.[78]

Temperature has some effect on HPICs only if one of the blocks of copolymers is thermosensitive.[149] This is indeed the case for PNIPAM. With the PNIPAM-b-PMA copolymer, PMA in interaction with calcium was found at the core of the micelles at temperatures below 30°C. Above 30°C, the core was made of condensed PNIPAM.[67] The PMEMA-b-PMOMP block copolymer also formed reverse or inverse micelles depending on the temperature and ionic strength.[65] Double-anionic block-polystyrene sulfonate and polyacrylate copolymer showed this structural inversion depending on the metal ions (Ca^{2+} , Sr^{2+} or Ba^{2+}) dispersed in solution.[52]

6. Applications

6.1 Chemical and photochemical catalysis

The metal trapped inside the HPIC structure may convey some chemical properties to the hybrid micelles, which can in particular play the role of catalysts. This has rarely been exploited, but to our knowledge, two papers reported the photocatalytic activities of HPICs in solution. In 2013, Zheng et al. demonstrated that HPIC containing ruthenium can be dispersed in the presence of methanol.[150] Under visible light irradiation, the HPIC micelles catalyzed the aerobic oxidation of thioanisole with a conversion of 99%. The main advantage was that the catalytic Ru HPICs can be recovered by ultrafiltration (without any detectable leaching of ruthenium). The main drawback was that the photocatalysis was somewhat slower with HPICs, presumably because reactive compounds should diffuse into HPICs to be oxidized. Such a limitation was also reported in a study on the photocatalytic properties of a Cu HPIC.[73] Copper could catalyze photoFenton-like reactions: in the presence of hydrogen peroxide and under UV irradiation, Cu^{2+} produced the reactive oxidant HO^\bullet , which oxidized the organic molecules dissolved in the solution. Cu HPIC has the advantage of behaving like a homogeneous system with all the well-known advantages compared to heterogeneous catalysis. Recently, experiments were

reported on iron(III) HPIC, which catalyzed a photoFenton reaction with better recyclability than simple iron ions.[88]

The catalytic properties of metal HPICs in which metal ions were used to form inorganic nanoparticles have also been reported in the case of a Au HPIC (for the catalytic reduction of nitroarene)[86] and Cd HPIC (leading to photocatalytic H₂ production).[58]

As seen in Figure 10, the Cd HPIC made of PiPrOX-b-PAGA copolymer led to CdS nanoparticles producing hydrogen much more efficiently than free CdS nanoparticles. This more than 10-fold better efficiency could be related to better substrate adsorption near the particles due to the polymeric surface layer but also to the hydrophilic nature of this layer, which should favor proton or water diffusion toward the CdS core.

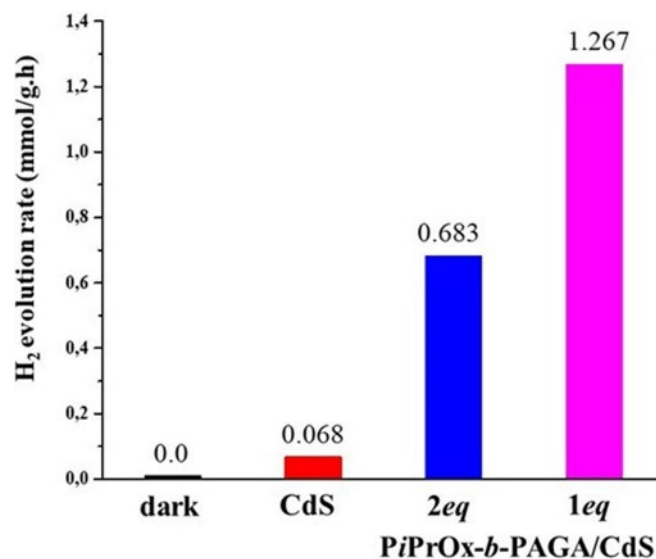


Figure 10: Influence of the system composition on the hydrogen evolution rate. Reprinted with permission from reference [58]. Copyright 2020 Elsevier.

6.2 Elaboration of (nano)material

In 1995, M. Antonietti et al. used polystyrene-*block*-poly(4-vinylpyridine) to organize gold ions into HPICs in toluene. The gold ions were then reduced by hydrazine to obtain noble metal colloids, which are promising catalysts for hydrogenation or organic reactions.[170] Unfortunately, no characterization of the possible association between the copolymer of the gold ions was performed at that time. In 1998, L.M. Bronstein and coll. used a similar strategy in water with gold, palladium and platinum ions and hydrazine or hydrogen to disperse metal nanoparticles in water and suggested the formation of pristine metal HPICs.[14] The idea was to use HPICs as a nanoreservoir of metal ions: this structure could then yield some control of nanoparticle formation. DHBCs also had the tendency to cap the surfaces of the formed nanoparticles, ensuring their colloidal stability. Two reviews illustrated the various nanomaterials that were synthesized before 2006 with DHBCs (with or without characterization of the possible HPIC formation).[171, 172] Metal and metal carbonate nanoparticles were mainly studied, together with calcium (oxalate or tartrate) or barium salt (chromate or tungstate).

Since 2006, noble metal (such as gold, silver and platinum) nanoparticles have continued to be synthesized starting from an HPIC system.[83, 85, 86, 94, 108, 132] For instance, the interaction of AuCl₄⁻ with PEO-b-PAA copolymer led to HPICs with an average diameter of 30 nm. Reduction of the gold ions enabled the formation of gold nanoparticles with a diameter close to 17 nm more or less independent of the polymer molecular weight. The colloidal stability of the final nanoparticles was much higher than that of the usual citrate gold nanoparticles due to the adsorption of the copolymers on their surfaces (see Figure 11).[85]

(a) Small Molecule Ligand



(b) Double Hydrophilic Block Copolymer

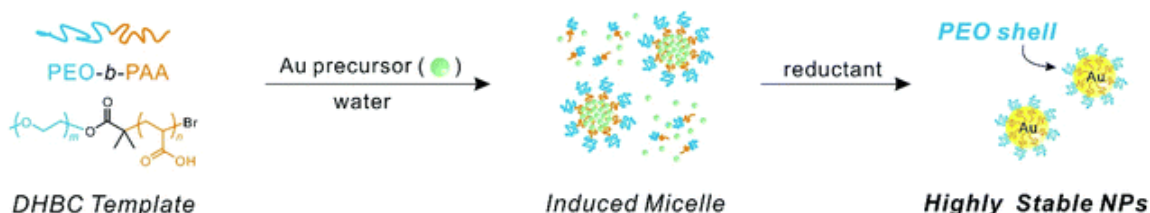


Figure 11: Synthetic pathway of gold nanoparticles using small molecules or HPICs and corresponding stability under various conditions. Reprinted with permission from reference [85]. Copyright 2017 Royal Society of Chemistry.

Y. Yamauchi et al. suggested that the DHBC PEO-b-poly(vinylpyridine) can be used to form mesopores inside metal nanospheres. Indeed, starting from Pt HPICs, after reduction by hydrazine, they obtained platinum nanospheres of ca. 40 nm with channels with a spacing of 0.23 nm.[108]

Metal oxide or hydroxide nanomaterials have also been synthesized using HPICs. The addition of diazine to Ru HPICs yielded nanoparticles of ruthenium oxide that were stable for several months in solution and, after annealing at 400°C, exhibited high capacitance.[130] Pure iron oxide or mixed Co/Fe oxides have also been constructed.[87, 152] Mixed Cu/Al or Mg/Al layered double hydroxides were obtained after the mineralization of HPIC micelles: the final nanoparticles had a mean diameter that was adjusted by the polymer and have a high colloidal stability useful for potential applications, for example, as drug delivery systems.[45, 47] A couple of examples concerning metal sulfides (cadmium or zinc) have also been reported in the past few years.[58, 59, 134] Finally, a DHBC mixed with metal ions led to metal phosphate by the fast addition and mixing of reactive solutions.[173, 174]

In conclusion, a recent attempt to use HPICs as starting confined systems for the controlled formation of Prussian Blue should be noted.[175] Future work may try to extend this strategy to many other molecular materials with a large range of potential applications.

6.3 Biological studies

Since the pioneering work of K. Kataoka, a large number of papers have dealt with biological or medical applications of hybrid micelles. Kataoka's review in 2018 on block copolymer micelles described in particular the anticancer applications of HPICs loaded with platinum.[176] A more general review on DHBCs also created an interesting perspective of the medical applications of DHBC and thus also HPICs.[9] Since these two reviews provide many details of the biological studies of HPICs, we will just provide in the following paragraphs some of the main useful characteristics of hybrid micelles for biomedical applications.

As already mentioned, an interesting feature of HPICs is the possibility of controlling their mean size through mixing with a homopolymer. The effect of the nano-object size on biological features can therefore be simply studied. A nice example of this is given in Kataoka's paper.[126] Mixing the diblock copolymer PEO-P(Glu) with the homopolymer P(Glu) and platinum ions led to HPICs with a diameter in the range of 30 to 110 nm depending on the ratio of homopolymer to diblock copolymer. Regardless of the mixture composition, the zeta potentials of the assemblies were close to zero, suggesting that the neutral HPIC shell was maintained for all sizes. The *in vitro* cytotoxicity was equivalent for all diameters. Taking into account such data, K. Kataoka and coll. analyzed the effect of the particle size on the accumulation and effectiveness of micelles. No size effect concerning the

permeability of HPICs in hypervascular tumors was detected. However, in the case of hypovascular tumors, only HPICs with a diameter smaller than 50 nm could penetrate the tumors.

HPICs are also polymeric aggregates that one can easily modify to functionalize their surface with various biologically relevant functional groups. To achieve such functionalization, researchers have synthesized copolymers with one PEO block terminated by a chemical functional group, such as maleimide[107, 118, 123] or catechol.[110, 124] After the formation of these HPICs, reaction with a thiol or boronic acid led to the conjugation of the biochemical molecules to the surfaces of the HPICs. The percentage of functionalized polymers was often estimated through NMR and was adjusted between 0 and 60% by changing the experimental parameters. In addition to fluorescent dye, folic acid was attached to the HPIC surface,[110, 118] as well as sialic acid,[124] a short peptide[123] or an antibody fragment.[107] Analysis of the HPIC toxicity before and after conjugation is often performed, and the results are highly dependent on the types of biologically relevant functional group and cell lines. Clearly, this strategy - conjugation after HPIC formation - could lead to nano-objects with a large range of biological activities.

As stated previously, the release of drugs using HPICs has been largely studied. *In vivo* experiments based on Pt HPICs have clearly demonstrated the interesting ability of the HPIC structure to limit the side effects, control the speed of platinum release and enhance the antitumor effect of cisplatin.[97, 102, 103, 105, 111, 114, 120, 121, 123, 128] In addition to platinum, the HPIC structure was tested for other metal or drug transport and release. For example, hybrid micelles formed with cadmium were assessed by An et al. for antitumor activity.[57] With a cadmium load of ca. 34% w/w, the HPICs released a majority of the metal ions in less than 10 h, inducing clear *in vitro* cytotoxicity. In addition to using the toxicity of the metal ions trapped within the HPICs to obtain bioactive materials, a second simple strategy consists of loading the final hybrid micelles with bioactive molecules. For instance, the well-known molecule doxorubicin was encapsulated in HPICs through interactions between the polymers and the amine functional groups of this compound.[60, 91, 177] Up to 86% by weight of doxorubicin could be loaded in HPICs, and its release depended on the pH and possible cross-linking of the hybrid micelles. The kinetics of release often exhibited two regimes: a fast regime in the first few hours and a slow regime in the next few days. Dactolisib (a dual inhibitor of phosphatidylinositol-3-kinase),[116] 5-fluorouracil (used to treat cancer),[54] or the Alexa 680 dye[122] were also trapped inside HPICs to incorporate the final system with biological materials.

In the past decade, the HPIC system has also been studied as a new contrast agent for biomedical imaging. The loading of hybrid micelles with a dye or forming HPICs with fluorescent macromolecules allows one to easily build structures for fluorescent imaging.[122, 146, 178] Manganese[92, 179] or gadolinium[78, 80, 177] ions led to HPICs with metallic ions providing interesting properties for magnetic resonance imaging (MRI). In particular, the large size of the hybrid micelles in comparison with the ion radius increased the rotation time of the contrast agent, which was much more efficient than the simple metal ion complex. *In vivo* experiments[78, 146, 177] have shown the biocompatibility of HPIC architectures and their excellent properties for MRI. Other systems with gallium have been designed for positron emission tomography (PET) but have not yet been tested *in vivo*. [81]

Finally, one should emphasize that the chemical stability of HPICs in the presence of proteins (*in vitro* or *in vivo*) has been scarcely analyzed (for example, see reference [146]), as well as the possible exchange with endogenic metal ions. These points should be more carefully studied in the near future for all biological HPIC applications.

7. Conclusion

DHBC association with metal ions is a class of polymeric organized systems with numerous properties pertaining to chemistry, (nano)material science and biological and medical science. This class has seen a great amount of progress in terms of the characterization of their structures and their applications in recent decades. As indicated in this review, they are often surprisingly monodisperse in size and have a micellar structure. By varying the metal and polymer natures, various structures, including vesicles, may also be obtained. A large number of other metal ions or a variety of polymers could clearly be used in the near future, expanding the scope of HPIC applications. Stimuli-sensitive systems, “schizophrenic” behavior, and the template effect have been poorly or not at all studied with HPICs, leaving many opportunities for constructing new “intelligent” systems. Conditions of HPIC formation are still partially unknown and cannot be estimated by theoretical

studies of such association based on multivalent ions, studies which are unfortunately very scarce. This should be related to the difficulties in correctly simulating ion complexation and interactions with polymer pendant functional groups. In addition to an ever enhancing characterization of the HPIC structure, many questions still remain. For example, the kinetics of HPIC formation and dissociation, architecture stability under various chemical conditions, exchanging of macromolecules or metal ions, etc., are still poorly understood and analyzed. We hope that this review will stimulate researchers to work on this field, to promote new applications of HPICs and to compare them with the more classical organized structures obtained either with amphiphilic compounds or with polyanion/polycation associations.

Supplementary information

Figure S1: Covariance matrix between all the experimental parameters and HPIC observations (in green positive covariance, in red negative covariance).

Ion charge: Charge of the metallic ions

Dpt: sum of the degrees of polymerization of the neutral block and the charged block.

Dpn: degree of polymerization of the neutral block.

Dpi: degree of polymerization of the ionic block.

Dh (Int): hydrodynamic diameter (in intensity) measured by DLS.

Nagg poly: mean number of polymers aggregated in one HPIC nano-object.

Dc: Diameter of the HPIC core determined by TEM, SAXS or SANS.

	Ion charge	Dpt	Dpn	Dpi	Dh _(int)	Nagg poly	Dc
Ion charge	1	0.08945547	0.1623624	-0.18352005	0.05575197	-0.49506621	-0.06494274
Dpt	0.08945547	1	0.94925226	0.50703617	0.36857119	-0.3083456	-0.14369834
Dpn	0.1623624	0.94925226	1	0.21196533	0.34854187	-0.40247073	-0.11832475
Dpi	-0.18352005	0.50703617	0.21196533	1	0.24492599	0.14661149	-0.11314669
Dh _(int)	0.05575197	0.36857119	0.34854187	0.24492599	1	0.6099209	0.34558903
Nagg poly	-0.49506621	-0.3083456	-0.40247073	0.14661149	0.6099209	1	0.25516027
Dc	-0.06494274	-0.14369834	-0.11832475	-0.11314669	0.34558903	0.25516027	1

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