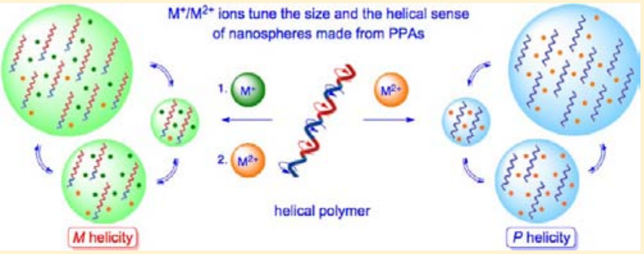
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Nanospheres with Tunable Size and Chirality from Helical Polymer–Metal Complexes

Félix Freire, José Manuel Seco,* Emilio Quiñoá, and Ricardo Riguera*

Department of Organic Chemistry and Center for Research in Biological Chemistry and Molecular Materials (CIQUS), University of Santiago de Compostela, E-15782 Santiago de Compostela, Spain

Supporting Information



ABSTRACT: A new family of nanospheres is made by complexation of divalent metals (i.e., Ca^{2+}, Ba^{2+}) and poly(phenylacetylene) polymers bearing α-methoxyphenylacetic acid (MPA) pendants with high content of the cis isomer responsible for their helical structures. The resulting helical polymer–metal complex (HPMC) nanospheres present two interesting properties: (a) their diameter can be tuned to different sizes, to growth or to shrink, by changing the metal ion or the polymer/metal ion ratio, and (b) the helicity on the surface and the interior of the particle can be tuned to any of the two helical senses (*M* or *P*) by selection of the metal ion. The role of the solvent, the metal ion, and the helicity of the polymer in the aggregation are discussed. The ability of these nanospheres to encapsulate is demonstrated with examples.

INTRODUCTION

In the past decade, the use of supramolecular self-assembly for the generation of diverse kinds of ONPs[1] (organic nanoparticles) and MOFs[2] (metal organic frameworks) has experienced an intense development. This is basically related to their encapsulating properties allowing the utilization of functional structures encapsulated inside micro- and nanomatrices in fields such as material sciences,[3] nanoreactors,[4] diagnostic tools,[5] cosmetics, and drug-delivery.[6]

Among other approaches, the preparation of polymeric nanoparticles by aggregation of polymeric chains via intramolecular covalent or noncovalent cross-linking is a relatively new technology.[7] Although a large variety of polymeric matrices have been used to date to encapsulate a wide range of chemical structures,[8] helical polymers based on poly(phenylacetylene)[9] frameworks have not been explored as potential capsules.

In a recent work,[10] we described that poly(phenylacetylene)s poly-**1** and poly-**2** [with (*R*)- and (*S*)-α-methoxyphenylacetic acid (MPA) respectively, as chiral pendants and high content of the cis isomer[11]], in solution are composed of a 1:1 equilibrium mixture of both helical senses (*M* and *P*) originating a null CD for both polymers.[12]

Interestingly, when these polymers are dissolved in noncoordinating solvents (i.e., $CHCl_3$) and some metal cations are added, the equilibrium is shifted to a preponderant helical sense. This helix induction is selective for the type of metal ion and requires low amounts of metal for the helix to appear due to chiral amplification.

Extensive studies (AFM, CD, IR, theoretical calculations) demonstrated that the origin of this process lies on the selective and reversible coordination of mono- and divalent metal cations on the pendants (MPA part) of the polymer and the subsequent modification of its conformational characteristics.

Thus, in solution, the MPA pendants are in equilibrium between two main conformations [synperiplanar (*sp*) and antiperiplanar (*ap*)] in 1:1 ratio approximately and the polymer is constituted by a 1:1 mixture of the two helical senses, showing a null CD response.

When coordination with a monovalent cation (i.e., Ag^+), takes place, the MPA pendants adopt an antiperiplanar conformation (*ap*) that is transmitted to nearby pendants (with amplification of chirality), and the helix backbone adopts a predominant helical sense [i.e., left-handed in the case of (*R*)-MPA (poly-**1**) and right-handed with (*S*)-MPA (poly-**2**)]. On the other hand, a divalent cation (i.e., Ba^{2+}) favors the synperiplanar (*sp*) conformation that is transmitted by chiral amplification to the backbone, resulting in the opposite predominant helical sense [i.e., right-handed in the case of (*R*)-MPA (poly-**1**) and left-handed with (*S*)-MPA (poly-**2**)].

Therefore, the different structure and steric requirements of the complexes with mono- and divalent ions are transmitted to the polymer backbone, with intense amplification of chirality [cation (mol)/monomer repeat unit (mol) ≤ 0.1 is enough to induce the maximum CD response], converting these materials in efficient sensors for the valence of the metals (Figure 1).

We now report that stable nanospheres with tunable size and helicity can be obtained when divalent metal ions are added to poly-**1** and poly-**2**, in the presence of donor solvents (i.e., THF, acetone). We will show also that this phenomenon goes through the complexation between the polymer and the cation

Received: June 28, 2012
Published: August 15, 2012

dx.doi.org/10.1021/ja3061112 | J. Am. Chem. Soc. 2012, 134, 19374−19383

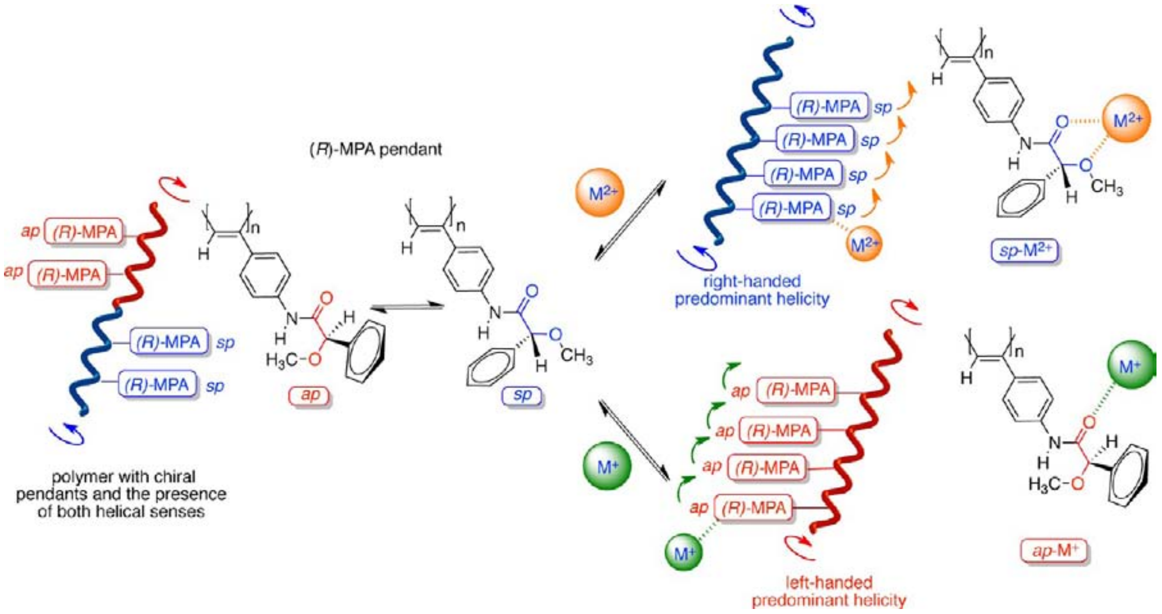


Figure 1. Representation of the (*R*)-MPA polymer (poly-**1**) and the conformation of the pendants before and after coordination with mono- and divalent metal cations in noncoordinating solvents (i.e., $CHCl_3$). The bonds that define the synperiplanar (*sp*) and antiperiplanar (*ap*) conformations are highlighted. A conceptual model of the amplification phenomenon indicating the *ap*/*sp* conformation of the pendants has been included.

and the formation of a helical polymer–metal complex (HPMC), where the metal cation controls the self-assembly of the polymer, its chirality (helicity), and the morphology/size of the nanostructures. The resulting nanospheres are able to encapsulate a variety of guests, such as quantum dots, fluorescent dyes (5,6-carboxyfluorescein, rhodamine B isothiocyanate), and iron oxide magnetic particles.

■ RESULTS AND DISCUSSION

DLS studies and diverse electron microscopy techniques on poly-**1** and poly-**2** showed that these polymers in $CHCl_3$ and THF do not form, just by themselves, any type of defined particles.

Nevertheless, when divalent cations were added to a solution of the polymers in $CHCl_3$, aggregation took place, giving first unstable nanospheres with nonhomogeneous size distribution that immediately evolved to large 2D and 3D networks.

Interestingly, when THF solutions of poly-**1** and poly-**2** and perchlorates of divalent metals [$M(ClO_4)_2$; M = Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Ba^{2+}, Hg^{2+}, Pb^{2+}] were mixed together, stable and well-defined spherical particles with very good PDI values, were produced (see CD spectra in Figure 2 and other CD and DLS studies in the Supporting Information). Similar good quality nanospheres could be obtained in $CHCl_3$ if a small volume of a donor solvent, such as acetone or THF, were added to the $CHCl_3$.

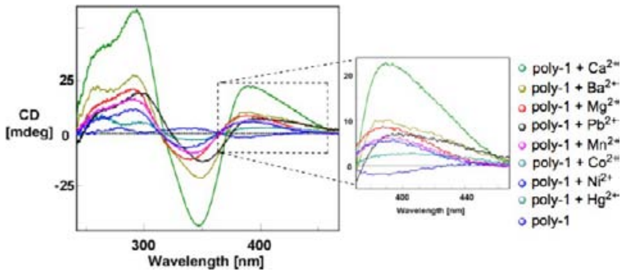


Figure 2. CD spectra of poly-**1** and its HPMCs with diverse divalent metal cations in THF (0.1 mg/mL of polymer; saturated solutions). Enhanced partial CD spectra of the vinylic region is shown.

These nanospheres present two outstanding characteristics:

(a) Their average diameter[13] can easily be tuned up to a different size, increasing or decreasing in a controlled way (Figures 3 and 4) by changing the metal ion or the polymer/ion ratio.

(b) The helicity of its components, the outside (surface) and inside (core) of the nanosphere, can be tuned to be right-handed or left-handed by selection of the starting polymer. Also, a single polymer can be compelled to produce right-handed or left-handed helically oriented nanoparticles just by adequate use of mono and divalent ions (vide infra).

The role of the solvent, the metal ion, and the helicity of the polymer on that aggregation, are discussed next.

Tuning the Size of the Nanospheres. The addition of perchlorates of divalent metals to solutions of poly-**1** or poly-**2** in THF at an appropriate polymer(mru)/M^{2+} ratio originates the appearance of well-defined nanospheres [i.e., a poly-**1**(mru)/Ca^{2+} ratio of 1.0/1.0 generate nanospheres of 100 nm respectively; polymer concentration = 0.1 mg/mL].

Thus, when we modify the stoichiometric ratio between monomeric units of the polymer and the metal ion (mol/mol), larger particles are generated employing larger quantities of the metal salt versus polymer. For instance, in the case of the addition of the Ca^{2+} salt to poly-**1** or poly-**2** (polymer concentration = 0.1 mg/mL), we found that polymer(mru)/Ca^{2+} ratios of 1.0/1.0, 1.0/1.2 and 1.0/>1.2 generate nanospheres of 100, 160, and 200 nm, respectively.

Using a Ba^{2+} salt in ratios polymer(mru)/Ba^{2+} of 1.0/3.0, 1.0/4.0 and 1.0/5.0, nanospheres of 100, 140, and 170 nm respectively were obtained.

Thus, the sequential addition of metal ion salt to the polymer implies the sequential growth of the particles (Figure 3). The range of the tunable size for well-defined and stable particles goes from 80–90 nm (the lowest limit) to 200 nm (the highest).

Interestingly, this phenomenon can also be induced to take place in the opposite sense, that is, the sequential reduction of the particle size by the addition to pre-existent nanospheres of extra amount of polymer.

For example, the well-formed particles of 160 nm obtained by addition of Ca^{2+} salt to poly-**1** [poly-**1**(mru)/Ca^{2+} ratio of 1.0/1.2 (mol/mol), PDI 0.18] evolved—after addition of poly-**1** to a 3.0/1.0 ratio—into particles of 112 nm (PDI 0.20) that were further transformed into particles of 90 nm (PDI 0.20) by addition of another 1 mol of poly-**1** (Figure 4); analogous results were obtained with Ba^{2+} (see Supporting Information).

It is important to point out that neither the addition of the monomer [*N*-(4-ethynylphenyl)-2-methoxy-2-phenylacetamide] nor the addition of acetylacetone results in any diminution or increase on the size of calcium or barium nanospheres, thus suggesting that a cooperative effect caused by the polymer is necessary for the event to take place.

As mentioned before, the size of the HPMC nanospheres depends not only on the ratio of polymer/ion, but also on the nature of the metal ion giving the complexation, and accordingly, the ratio polymer(mru)/M^{2+} (mol/mol) needed to form particles of a given size, is characteristic for each metal ion.

In this way, in order to form 100 nm diameter nanospheres, a 1.0/1.0 ratio is necessary with Ca^{2+}; but a 1.0/3.0 ratio is required to obtain the same size nanospheres with Ba^{2+}.

The Stability of the Nanospheres. The formation of the nanospheres is usually monitored by DLS, but can also be followed by CD. Thus, when the divalent ion is added to the polymer in THF, the CD band shows a small increase of intensity, but it is not until a certain ratio polymer/ion is attained that the nanoparticles appear (Figure 5). This ratio is specific for every ion [i.e., polymer(mru)/M^{2+} of 1.0/1.0 for

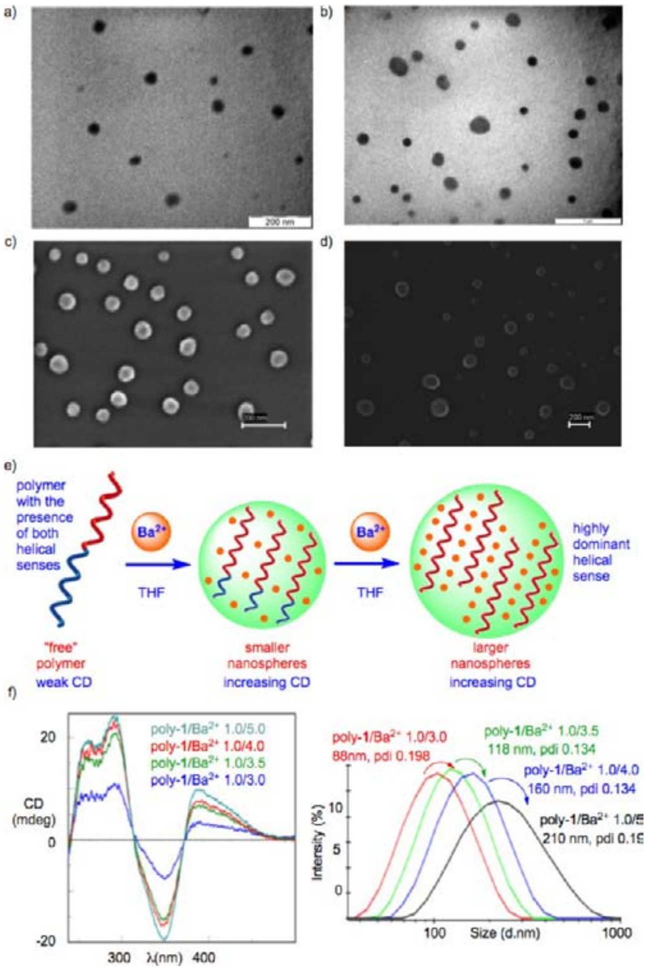


Figure 3. TEM images of HPMC nanospheres (THF, 0.1 mg polymer/mL): (a) poly-**1**(mru)/Ba^{2+} = 1.0/3.0 (mol/mol) (92 ± 15 nm, 50 particles, scale bar 200 nm) and (b) poly-**1**(mru)/Ca^{2+} = 1.0/1.3 (mol/mol) (140 ± 30 nm, 25 particles, scale bar 1 μm). FE-SEM images of HPMC nanospheres: (c) poly-**1**(mru)/Ba^{2+} = 1.0/3.0 (mol/mol) (81 ± 10 nm, 30 particles, scale bar 200 nm) and (d) poly-**1**(mru)/Ca^{2+} = 1.0/1.3 (mol/mol) (120 ± 30 nm, 30 particles, scale bar 200 nm). (e) Conceptual representation of the formation and evolution of HPMC nanospheres. (f) CD spectra and DLS traces on going from poly-**1**(mru)/Ba^{2+} = 1.0/3.0 to 1.0/5.0 (mol/mol).

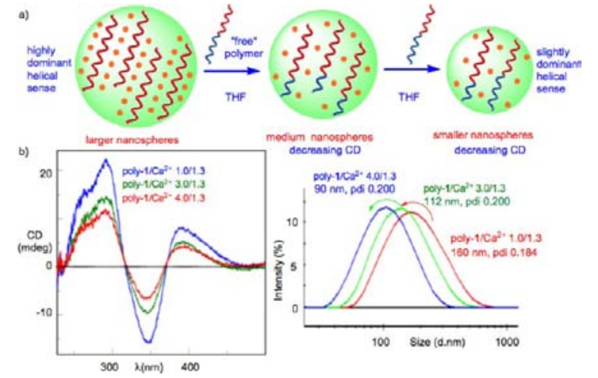


Figure 4. (a) Schematic representation of the evolution of HPMC nanospheres by addition of "free" polymer. (b) CD spectra and DLS traces on going from poly-**1**(mru)/Ca^{2+} = 1.0/1.3 to 4.0/1.3 (mol/mol). Both the dominant helical sense and the size diminish.

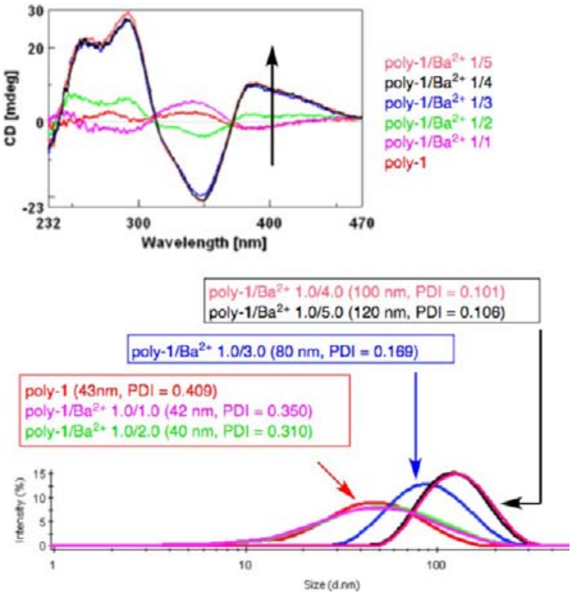


Figure 5. CD and DLS traces of the evolution of poly-**1** (0.1 mg/mL in THF) during the sequential additions of Ba^{2+} (1 mol of cation per mole of mru in each addition). Both the CD and DLS traces remain virtually unchanged from 0 to 2 mol until a noticeable "jump" is produced when 3 mol of cation per mol of mru is added and the nanospheres appear.

Ca^{2+} and 1.0/3.0 for Ba^{2+}]. For the nanospheres to reach their final stable size, a period of at least 1 hour after mixing the polymer and the ion salt is necessary. This evolution can be monitored by DLS. For instance, when a solution of poly-**1** is mixed with Ba^{2+} salts in a ratio of 1.0/4.0 {polymer(mru)/M^{2+}; [poly-**1**] = 0.1 mg/mL}, nanospheres of 71 nm diameter are detected 5 min after mixing, but 1 h is necessary for the particles to reach their final and larger morphologies (≈100 nm) (Figure 6).

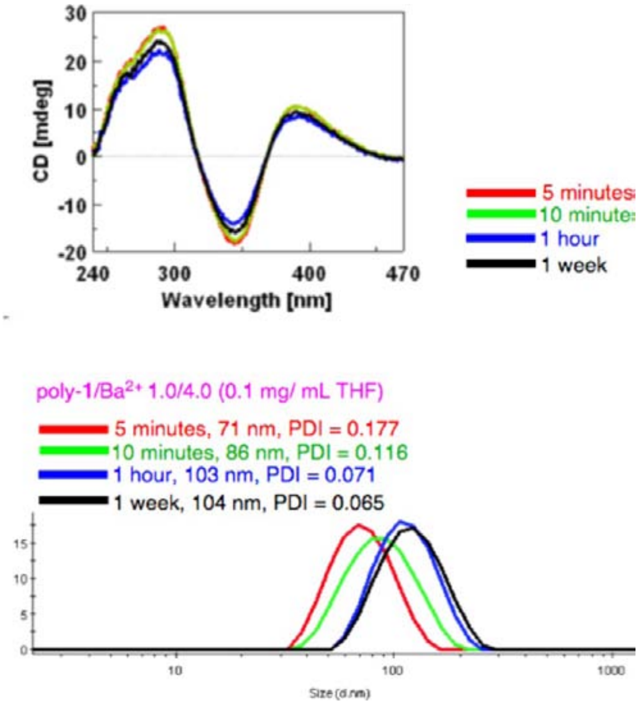


Figure 6. CD and DLS traces showing the evolution of barium nanospheres in THF. The final size is reached after approximately 1 h and remains stable for weeks.

As for their stability with time, we observed a clear dependence on their size and on the metal ion involved. The Ca^{2+} and Ba^{2+} nanospheres with diameter shorter than 200 nm were shown to be stable in THF for periods longer than 1 month, but the stability of particles with larger diameters was shorter due to the appearance of aggregation phenomena. Other HPMC particles were found to be stable for just a few hours, depending on the nature of the metal (i.e., Pb^{2+}, Hg^{2+}, or Mn^{2+}).

As we mentioned at the beginning of this paper, the presence of donor solvents is necessary for the aggregation to produce stable, homogeneous nanospheres, so apart from the results in THF just described, we investigated also how other donor solvents could affect the aggregation.

Thus, when the particle formation was carried out in net acetone, the resulting nanospheres behave differently to those prepared in net THF.

The nanospheres obtained from poly-**2** and Ba^{2+} in acetone present similar size to those from THF, but in contrast, their diameters do not depend on the ratio polymer(mru)/M^{2+} nor does the size/morphology (FESEM, AFM) change by addition of more ion salt. So, particles of just 70−100 nm are formed for any of these poly-**2**(mru)/Ba^{2+} (mol/mol) ratios: 1/1, 1/3, 1/10, 1/20, and 1/50 (Figure 7). In fact, in acetone, nanospheres never reached a size large enough to form nanonetworks.

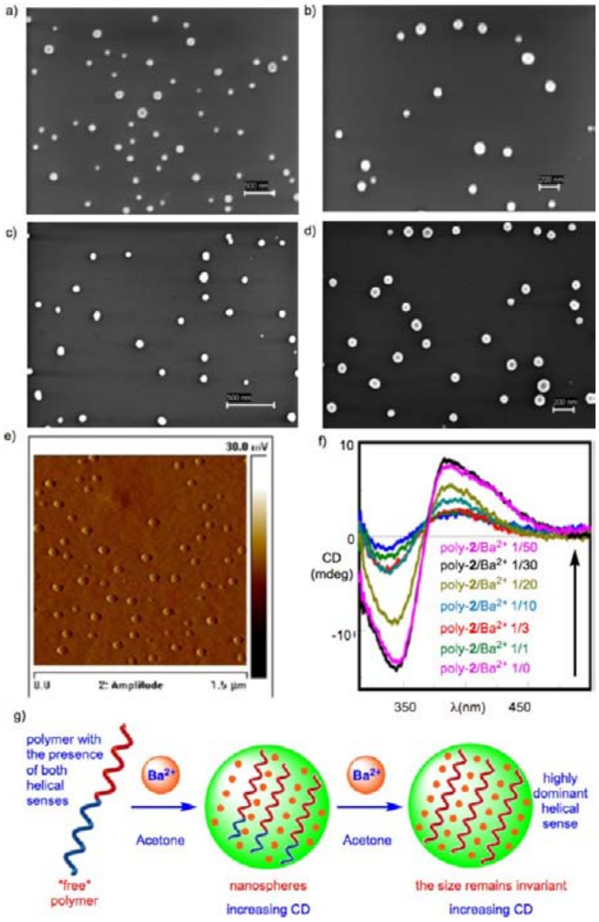


Figure 7. FESEM images of HPMC nanospheres (acetone, 0.1 mg polymer/mL): (a) poly-**2**(mru)/Ba^{2+} = 1.0/1.0 (mol/mol) (99 ± 18 nm, 50 particles, scale bar 500 nm), (b) poly-**2**(mru)/Ba^{2+} = 1.0/5.0 (mol/mol) (75 ± 18 nm, 50 particles, scale bar 500 nm), (c) poly-**2**(mru)/Ba^{2+} = 1.0/10.0 (mol/mol) (79 ± 12 nm, 50 particles, scale bar 200 nm), and (d) poly-**2**(mru)/Ba^{2+} = 1.0/20.0 (mol/mol) (90 ± 16 nm, 50 particles, scale bar 200 nm). (e) AFM image of HPMC nanospheres (acetone, 0.1 mg polymer/mL): poly-**2**(mru)/Ba^{2+} = 1.0/10.0 (mol/mol) (70 ± 148 nm, 35 particles, scale bar 1.5 μm). (f) CD spectra of poly-**2** (acetone, 0.1 mg polymer/mL) with different amounts of $Ba(ClO_4)_2$. (g) Schematic representation of the evolution of HPMC nanospheres in acetone.

Interestingly, although the size of the particles does not change by addition of more ion, the intensity of the CD band increases proportionally to the amount of metal salt added (Figure 7f). In other words, in acetone, the repeated additions of Ba^{2+} do not modify the size of the nanospheres but increase the helicity of the polymeric components.

Experiments on the formation of these nanoparticles were also carried out in mixtures of $CHCl_3$/MeOH and $CHCl_3$/acetone, revealing that the presence of a small amount of the donor solvent acts as a stabilizer of the nanoparticles, preventing their uncontrolled collapse to nanonetworks, as is observed in net $CHCl_3$ (Figure S26a,b, Supporting Information).

This stabilization is important enough to efficiently block the collapse of even the larger (around 200 nm) and less stable nanoparticles in THF.

Thus, the addition of a small amount of acetone (50 μL) to the nanospheres obtained from poly-**2**/Ba^{2+} in THF (0.1 mg of poly-**2**, 1.0 mL of THF, 5.0 mol of Ba^{2+} per mol of mru) generates stable (>3 weeks) particles of ≈215 nm (Figure S26c, Supporting Information). Other ketones (i.e., benzylacetone, 4-phenylbutan-2-one) produced analogous effects.

Tuning the Helicity of the Nanospheres. The helicity of the polymers assembling the spheres is particularly significant, as most uses of nanoparticles involve recognizing processes on the surface of the particle (i.e., drug delivery) or inside cavity (i.e., nanoreactors), making the chirality of those areas of utmost interest. This helicity can be easily inferred in solution from the CD spectra.[14] So, while free polymers poly-**1** and poly-**2** give virtually null CD due to their particular composition [a 1:1 ratio of both helical senses), the nanospheres produced by addition of a M^{+2}, such as Ca^{2+}, to poly-**1** (or **2**) in THF, present strong Cotton effect (Figure 2] at the vinylic region, indicating the presence of a dominant helical sense in the just formed HPMC that constitute the nanoparticle.

The other divalent metals also gave the same CD band but with lower intensity than Ca^{2+} (Figure 2). This suggests that although the polymer adopts in all cases the same major helical sense, triggered by identical complexation mechanism, the percentage of the major sense varies with the ion. Therefore, one should assume that, probably, polymer with the opposite helicity (the minor one, not shifted by complexation) is also present to some extent in the nanoparticle.

These results might indicate also that the presence of a single helix sense is not a must for the formation of stable nanospheres with good PDI, putting on the table the role of the helicity of the HPMC in the aggregation.

In order to clear up this point, we decided to repeat the aggregation experiments using mixtures of poly-**1** and poly-**2**.

In this way, we found that the addition of Ca^{2+} or Ba^{2+} to mixtures of poly-**1** and poly-**2** in different ratios in THF gave in fact nanospheres with morphologies similar to those of particles made by only one polymer. The CD spectra corresponded to the ratio of the polymers used (i.e., in a 1:1 mixture of both polymers, the CD spectrum obtained was null; Figure 8), indicating that both components are incorporated into the particles and that these are formed irrespective of the helicity of the starting polymer. No majority rule effect took place during the self-assembly of enantiomeric polymers (see a full description in the Supporting Information, Figure S24).

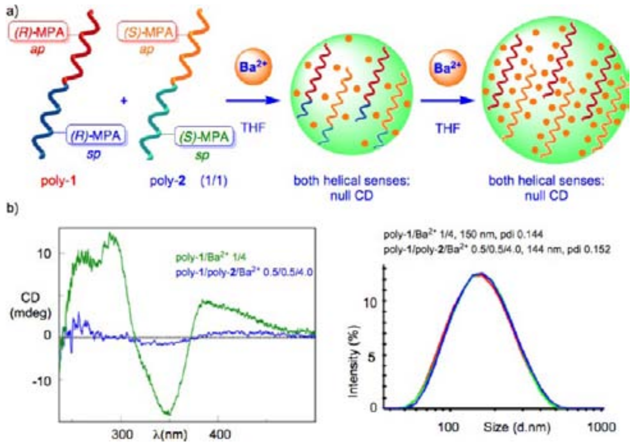


Figure 8. (a) Schematic representation of the formation of HPMC nanospheres made by poly-**1** and poly-**2** mixtures. (b) CD spectra and DLS traces of poly-**1**(mru)/Ba^{2+} = 1.0/4.0 (mol/mol) and poly-**1**(mru)/poly-**2**(mru)/Ba^{2+} = 0.5/0.5/4.0 (mol/mol/mol). The CD is canceled in the case of the 1:1 mixture of polymers, although the nanospheres present the same size as the single polymer nanospheres.

Next, we focused on the growth/reduction experiments and checked the results when they are performed with mixtures of polymers and found the process to be governed by the same principles as those operative with nanospheres made by single polymers (just poly-**1** or poly-**2**). Thus, in the growth experiments, when extra amounts of salt are added to nanospheres made by addition of M^{2+} to mixtures of poly-**1** and poly-**2**, the CD bands reflect the contribution from the helicity of both polymers. In 1:1 mixtures, the CD is null, all along the sequential additions of the salt; in other mixtures, the CD reflects the ratio between the polymers. However, the diameter increases according to the effect of the extra ion incorporated into the HPMC particle.

In the reduction experiments, when large particles formed by M^{2+} and a single polymer (i.e., poly-**1**) are submitted to the addition of an extra amount of the other polymer (i.e., poly-**2**), the CD bands of the particles diminish in accordance with the new polymer/ion ratio and their size decreases (Figure 4). For instance, CD and DLS monitoring of nanospheres made from 1 mol poly-**1**(mru) and 4 mol of Ba^{2+} showed that the subsequent addition of poly-**2** [starting with 0.1 mol (mru) and finishing with 2 mol (mru)] diminished both the CD response and the size (Figure S27, Supporting Information). At the final addition of 2 mol of poly-**2**(mru), the nanospheres broke up.

In resume, it seems clear that the degree of preponderance of a certain helical sense in the starting HPMC is not important at all with regard to nanoparticle formation, size, homogeneity, and stability. Both the HPMC formed from poly-**1**, poly-**2**, and their mixtures can be used to give good particles, but the chirality of their components, represented by the helicity of the HPMCs, is different.

According to these properties, two ways can be envisioned for the preparation of nanoparticles with tunable helicity, that is to say, with right- or left-handed helical components.

(a) The simplest one is to prepare them from polymers of opposite chirality at the pendant. Thus poly-**1** [(*R*)-MPA pendant] with M^{+2} produces HPMCs with right-handed helical sense (*P*), and the corresponding nanoparticles conserve that helicity. On the other hand, poly-**2** [(*S*)-MPA pendant] gives HPMCs and nanoparticles with left-handed helicity (*M*) (Figure 9).

(b) A more practical and elaborate approach makes use of the different response of these polymers to complexation with monovalent and divalent ions in $CHCl_3$ or $CHCl_3$/THF mixtures. As mentioned in the Introduction, the complexation of the MPA pendants with M^+ promotes the *ap* conformer in the pendant instead of the *sp* as happens with M^{2+}. This difference allows a single polymer such as poly-**1** [(*R*)-MPA pendants] to shift to a right-handed helix by interaction with divalent ions or to the opposite left-handed helix with monovalent ions [the other way around with poly-**2**, (*S*)-MPA pendants] (Figure 1).

So, treatment of poly-**1** (null CD) with divalent cations (i.e., Ba^{2+}; M^{2+}/mru ≈ 0.25; THF/$CHCl_3$ 100 μL/mL) afforded nanospheres with right-handed helical sense (positive CD band

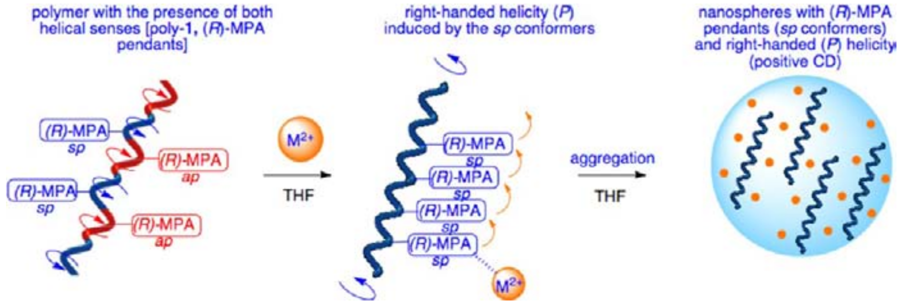


Figure 9. Preparation of nanospheres (*P* helicity, positive CD) from right-handed HPMCs originated by complexation of poly-**1** and divalent cations in THF. When HPMCs from poly-**2** (left-handed, enantiomeric pendants) are used, nanospheres with *M* helicity and negative CD are obtained. The relationship between nanospheres generated from both polymers can be termed as "enantiotopic" [(*R*)-MPA pendants/*P* helicity versus (*S*)-MPA pendants/*M* helicity].

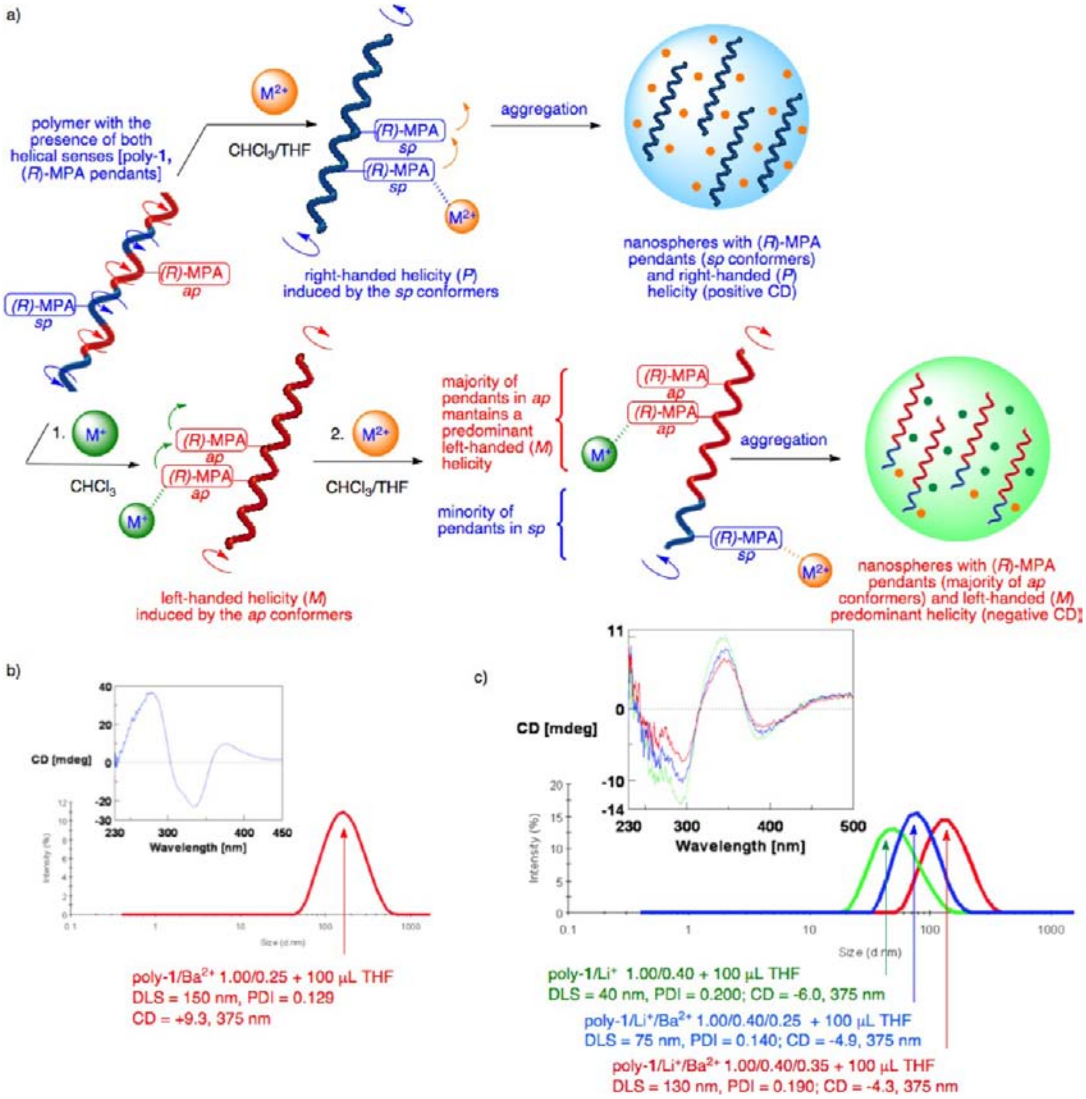


Figure 10. (a) Formation of nanospheres with right-handed and left- handed helicities and "diastereomeric" relationship [(*R*)-MPA pendants/*P* helicity versus (*R*)-MPA pendants/*M* helicity] from the same polymer (poly-**1**) in $CHCl_3$/THF. The complementary set of nanospheres [(*S*)-MPA pendants/*M* helicity versus (*S*)-MPA pendants/*P* helicity] is obtained starting with poly-**2**. (b) CD and DLS traces for the upper nanospheres (in blue). (c) CD and DLS traces for the lower nanospheres (in green). Polymer concentrations = 0.1 mg/mL; additions of 100 μL on 1 mL samples; ratios represent mol/mol and mol/mol/mol relationships for polymer(mru)/M^+ and polymer(mru)/M^+/M^{2+} respectively.

at 375 nm; diameter 150 nm) [Figure 10a(top),b]. When the same polymer was treated first with monovalent cations (i.e., Li^+; M^+/mru $\approx$ 0.40),[15] the expected left-handed helix induction without formation of nanospheres took place (negative CD response at 375 nm; pendants in *ap*). Subsequent additions of a divalent cation (i.e., Ba^{2+}; M^{2+}/mru $\approx$ 0.25 and 0.35) to that left-handed soluble HPMC led to the formation of nanospheres of larger size (75 and 130 nm respectively) that maintain the left-handed helical sense and the negative CD response dictated by the monovalent ion [Figure 10a(bottom),c].

Similarly, starting from poly-**2**, left-handed particles are obtained by direct addition of a divalent ion, but right-handed particles are prepared from the same polymer, by sequential addition of a monovalent ion (right-handed HPMC, no aggregation) and then a divalent ion (preserved right-handed helicity, aggregation). The CD spectra of the nanospheres prepared from Li^+ followed by Ba^{2+} showed analogous stability as those prepared just from Ba^{2+}.

To sum up, nanospheres with *M* or *P* helicities—and controlled sizes—can be obtained ad libitum from the same polymer depending on the addition of mono- or divalent cations.

The results presented in Figure 10, indicate that mono- and divalent cations play a separate role: monovalents act just on the helicity, shifting the conformational composition of the pendant to *ap* conformation and the backbone to a left-handed helix in the case of poly-**1**, while divalent ions promote both the *sp* conformation on the pendant and a right-handed helical backbone, together with nanoparticle formation.

Encapsulation inside the HPMC Particles. Having demonstrated the flexibility of these nanoparticles to be modulated in their size and chirality, we turned next to show their potential to encapsulate different types of chemical substances. To this end, we selected the following guests as examples that cover a wide variety of properties: iron oxide magnetic particles, quantum dots, and fluorescent dyes (5,6-carboxyfluorescein, rhodamine B isothiocyanate).

Following the protocol detailed in the Supporting Information, HPMC nanoparticles (i.e., formed by poly-**1**/Ba^{2+}) were prepared in the presence of ferromagnetic nanoparticles of iron oxide (10 nm) in THF or $CHCl_3$ as solvents, producing 150−200 nm nanospheres. In a parallel experiment, nanospheres without the guest were also synthetized as control.

DLS and CD experiments showed that in both cases (nanospheres with and without magnetic particles), the size and the CD spectra of the nanospheres were virtually the same (Figure 11), indicating that the encapsulation does not modify the mean size nor the helicity of the polymer.

The presence of iron oxide inside the resulting nanoparticles is shown in the TEM images as black dots absent in the control nanospheres, demonstrating that encapsulation had taken place (Figure 12).

Their magnetic properties are clearly shown when a magnet is placed close to the walls of a glass vial containing a $CHCl_3$ suspension. The migration of the nanospheres can be visualized until all the polymeric material ends up attached to the wall close to the magnet (Figure 11 and Supporting Information).

Experiments similar to those described above were carried out to encapsulate quantum dots (Lumidot CdSe/ZnS, 590 nm) and fluorescent dyes (5,6-carboxyfluorescein and rhodamine B isothiocyanate), and the process was monitored by confocal microscopy. Thus, while control nanospheres (without guest) present a weak fluorescence (see absorption and emission spectra of poly-**1** in the Supporting Information, Figure S25) and emit light green color (Figure 13a), the ones with fluorescein show a bright green emission (Figure 13b,c), and those with QDs (Figure 13d) or rhodamine (Figure 13e,f) emit a yellow-orange color as a result of the combination of red (QD or rhodamine) and the green emission of the polymer.

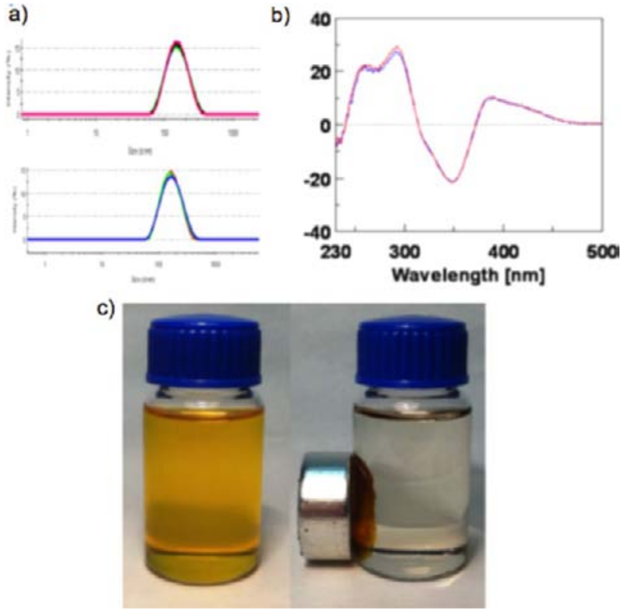


Figure 11. (a) DLS studies of poly-**1** nanospheres [0.1 mg/1 mL THF + Ba^{2+} (4 mol per mol mru)] before (red, top DLS trace; 150 nm, PDI = 0.120) and after (blue, bottom DLS trace) encapsulating magnetic nanoparticles (145 nm, PDI = 0.100). (b) CD spectra of poly-**1**/Ba^{2+} nanospheres before (red) and after encapsulating magnetic nanoparticles (blue). (c) Vial containing a suspension of HPMC nanospheres in $CHCl_3$ encapsulating magnetic nanoparticles before and after placing a magnet next to the wall.

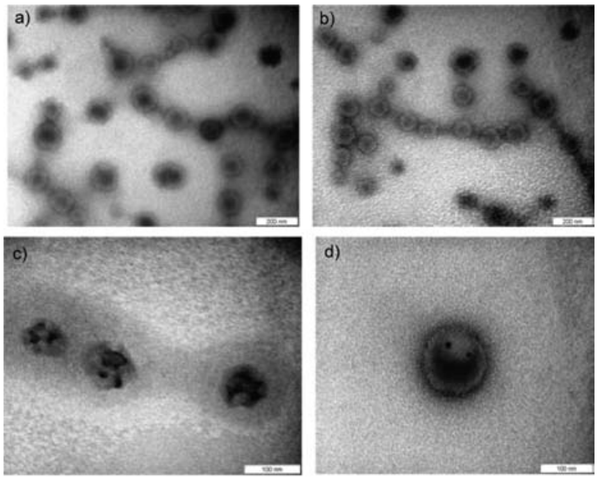


Figure 12. TEM images of HPMC nanospheres [$CHCl_3$ 0.1 mg polymer/mL, poly-**1**(mru)/Ba^{2+} = 1.0/0.3 (mol/mol) stabilized with 50 μL of MeOH] encapsulating 0.01 mol of iron oxide nanoparticles: (a) 119 nm ±12, 25 particles, scale bar 200 nm; (b) 114 nm ±11, 25 particles, scale bar 200 nm; (c) scale bar 200 nm; (d) scale bar 200 nm.

Role of the Metal Cation in the Aggregation. As shown before, polymers poly-**1** and poly-**2** just by themselves do not produce any type of aggregates. For aggregation to take place, a divalent metal cation must be added to the polymer, so the formation of specific HPMC with divalent ions is necessary.

Interestingly, aggregation of HPMCs takes place both from single polymers (just poly-**1** or just poly-**2**) or from mixtures of poly-**1** and poly-**2**. This fact expands the types of nanospheres that can be formed, thus making this methodology even more versatile. In both cases (one component or a mixture) and in

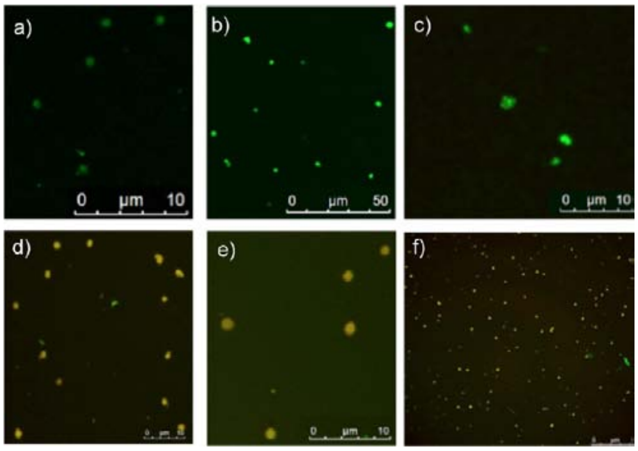


Figure 13. Confocal microscopy images of (a) HPMC nanospheres without any guest (λ_{exc} = 495 nm, λ_{em} = 505−540 nm), (b, c) HPMC nanospheres with 5,6-carboxyfluorescein (λ_{exc} = 495 nm, λ_{em} = 505−540 nm), (d) HPMC nanospheres with quantum dots (λ_{exc1} = 495 nm, λ_{em1} = 505−540 nm, λ_{exc2} = 590 nm, λ_{em2} = 600−700 nm), (e, f) HPMC nanospheres with Rhodamine B (λ_{exc1} = 495 nm, λ_{em1} = 505−540 nm, λ_{exc2} = 590 nm, λ_{em2} = 600−700 nm).

the presence of M^{2+}, nanospheres of the same size and stability are obtained.

The interaction between the polymer and the divalent ion is therefore the basic factor for the aggregation to be produced. In this sense, the effect of those ions[16] on the MPA moieties constituting the pendants of the polymer is well-known and serves as a model: monovalent ions bind with the oxygen of the carbonyl group, and that favors the *ap* conformation, while divalent cations complex to both the methoxy and the carbonyl groups and favor the *sp* conformer.

Thus, aggregation could result by the metal ion acting as a bridge between the pendants of different chains (Figure 14a). Experimental evidence (polymers with different sizes generate particles of similar sizes at similar concentrations and mru/M^{2+} ratios; the size of the particles increases when the concentrations of polymer or cation also increase) supports that intermolecular bonding is operative. In this hypothesis, only a few pendants need to be complexed with the metal to produced aggregates, as pointed out by the fact that in nondonor solvents such as $CHCl_3$, nanospheres begin to form at very low M^{+2}/mru ratios (i.e., 0.1). In donor solvents (THF, acetone), the addition of more ion is necessary because it is partially sequestered by solvation.

The formation of intramolecular linkages among pendants belonging to the same polymer chain (always mediated by the cations, as the polymer by itself does not aggregate at any concentration) must be also taken into consideration. Thus, intramolecular folding of fragments of the polymer below the persistence length of the helix could lead to the collapse of the chains to globular structures,[7a,b] in a fashion resembling those of globular proteins possessing α-helical segments or in other chiral globular structures such as dendritic crowns.[1b−d]

As the theoretical total length of a chain is, in general, longer (i.e., ≈350−500 nm) than the diameter of the nanospheres (i.e., ≈80−200 nm),[17] we can conclude that the polymers in fact do not adopt rodlike structures inside the particles and that intramolecular folding must take place to some extent (Figure 14b).

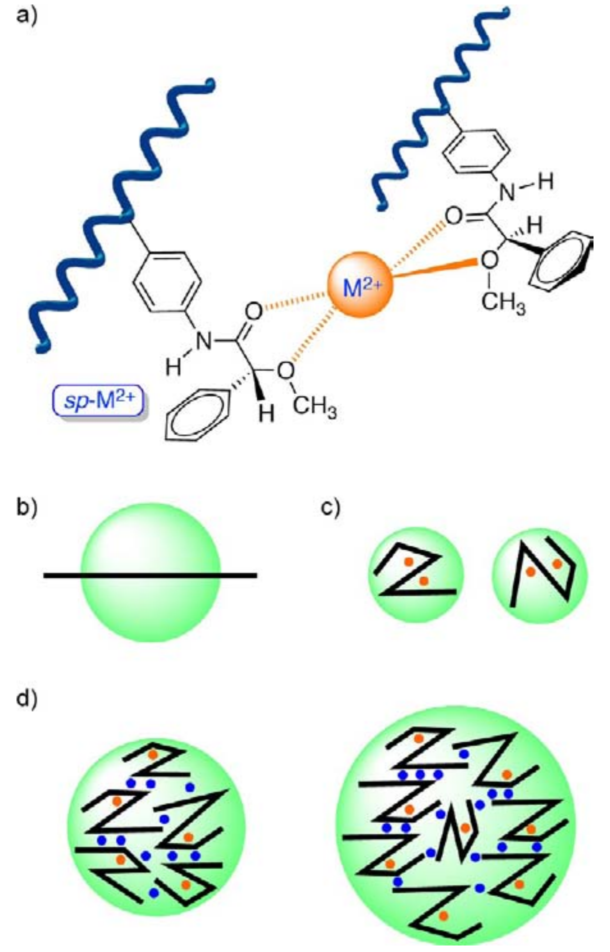


Figure 14. Conceptual representations of (a) the role played by divalent cations in the interlinkage between MPA pendants at *sp* conformation. Extra pendants and solvent molecules may be also involved (see ref 16). (b) Rodlike polymer (black) longer than the diameter of the nanosphere (green). (c) Nanospheres of similar sizes made by intramolecular folding of single polymer chains (in black). (d) Nanospheres of different sizes made by intramolecular folding and interlinking among different polymer chains. Orange and blue dots represent cations involved in intra- and intercomplexations, respectively.

However, globular structures made by the collapse of one single chain ("one chain nanospheres") can be ruled out on the basis of experimental facts: nanospheres do not reach the unique and stable size that would be expected if that were the case (Figure 14c).

So, a scenario where both intra- and interlinkages mediated by the cations coexist can be postulated (Figure 14d) as the origin of the globular structures.

■ CONCLUSIONS

In conclusion, we present a new class of nanospheres constituted by helical polymer−metal ion complexes (HPMCs). These are formed by addition of divalent cations to the polyphenylacetylenes poly-**1** and poly-**2**, and their size and helicity can be easily tuned.

The diameter can be selected by the use of an adequate metal ion or modifying the polymer/ion salt ratio. In this way, preformed nanospheres of certain size can be made to grow or to shrink to larger or smaller diameters.

The helicity of the HPMC forming the nanosphere, the outside and inner surfaces/cores, can be tuned to be right-handed or left-handed by selection of the starting polymer, but in addition, a single polymer can be made to produce right-handed or left-handed helically oriented nanoparticles just by adequate use of mono- and divalent ions.

Rational explanations for the helical changes and the aggregation process, based on the complexation of the pendants, the roles of the ions, the helicity of the polymer, and the solvent, are described.

The capability of these "tailor-made" chiral nanoparticles to encapsulate different types of materials opens the door to new supramolecular assemblies with controlled size and tunable chiral cores and surfaces that can be of great interest as functional matrices for encapsulation and recognition processes.

Although functional metal−organic particles have been prepared with a wide diversity of metal ions and/or organic ligands, to our knowledge this is the first time helical polymer metal complexes are exploited to produce functional nanoparticles.

ASSOCIATED CONTENT

Supporting Information

Extensive CD, UV−vis, DLS, SEM, and TEM studies on the formation of the nanospheres in THF and acetone; addition of scavengers; encapsulation of magnetic nanoparticles, fluorescent dyes, and QDs; X-ray and CD studies of the monomer of poly-**1**; poly-**1** absorption and emission spectra; stabilization of barium nanospheres by donor solvents; evolution of HPMC nanospheres by addition of enantiomeric polymer. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

ricardo.riguera@usc.es; josemanuel.seco@usc.es

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Ministerio de Ciencia e Innovación [CTQ2008-01110/BQU, CTQ2009-08632/BQU and Ramón y Cajal contract (F.F.)] and Xunta de Galicia (PGIDIT09CSA029209PR, CN2011/037) for financial support.

ABBREVIATIONS

AFM, atomic force microscopy; *ap*, antiperiplanar; CD, circular dichroism; CN, metal coordination number; DLS, dynamic light scattering; FESEM, field emission scanning electron microscopy; HPMC, helical polymer−metal complex; *M*, minus; MOF, metal organic framework; MPA, α-methoxyphenylacetic acid; mru, monomer repeat unit; ONP, organic nanoparticle; *P*, plus; PDI, polydispersity index; PPA, poly(phenylacetylene); QD, quantum dot; SEM, scanning electron microscopy; *sp*, synperiplanar; TEM, transmission electron microscopy; THF, tetrahydrofuran.

REFERENCES

(1) (a) González-Rodríguez, D.; Janssen, P. G. A.; Martín-Rapún, R.; De Cat, I.; De Feyter, S.; Schenning, A. P. H. J.; Meijer, E. W. *J. Am. Chem. Soc.* **2010**, *132*, 4710−4719. (b) Percec, V.; Imam, M. R.; Peterca, M.; Wilson, D. A.; Graf, R.; Spiess, H. W.; Balagurusamy, V. S. K.; Heiney, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 7662−7677. (c) Percec, V.; Imam, M. R.; Peterca, M.; Wilson, D. A.; Heiney, P. A. *J. Am. Chem. Soc.* **2009**, *130*, 1294−1304. (d) Percec, V.; Peterca, M.; Dulcey, A. E.; Imam, M. R.; Hudson, S. D.; Nummelin, S.; Adelman, P.; Heiney, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 13079−13094. (e) Horn, D.; Rieger, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4330−4361.

(2) (a) Imaz, I.; Hernando, J.; Ruiz-Molina, D.; Maspoch, D. *Ang. Chem. Int. Ed.* **2009**, *48*, 2325−2329. (b) Jung, S.; Oh, M. *Angew. Chem., Int. Ed.* **2008**, *120*, 2079−2081. (c) Wei, H.; Li, B.; Du, Y.; Dong, S.; Wang, E. *Chem. Mater.* **2007**, *19*, 2987−2993. (d) Maeda, H.; Hasegawa, M.; Hashimoto, T.; Kakimoto, T.; Nishio, S.; Nakanishi, T. *J. Am. Chem. Soc.* **2006**, *128*, 10024−10028. (e) Park, H.; Jang, K.; Son, S. U.; Sweigart, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 8740−8741. (f) Oh, M.; Mirkin, C. A. *Nature* **2005**, *438*, 651−654. (g) Sun, X.; Dong, S.; Wang, E. *J. Am. Chem. Soc.* **2005**, *127*, 13102−13103.

(3) (a) Nguyen, D.; Zondanos, H. S.; Farrugia, J. M.; Serelis, A. K.; Such, C. H.; Hawkett, B. S. *Langmuir* **2008**, *24*, 2140−2150. (b) Werts, M.; Badila, M.; Brochon, C.; Hébraud, A.; Hadziioannou, G. *Chem. Mater.* **2008**, *20*, 1292−1298.

(4) (a) Hashidzume, A; Harada, A. *Stimuli-Responsive Systems in Supramolecular Polymer Chemistry*; Harada, A., Ed.; Wiley-VCH: Weiheim, 2012; Chapter 11, pp 231−268. (b) Renggli, K.; Baumann, P.; Langowska, K.; Onaca, O.; Bruns, N.; Meier, W. *Adv. Funct. Mater.* **2011**, *21*, 1241−1259. (c) Monteiro, M. J. *Macromolecules* **2010**, *43*, 1159−1168.

(5) (a) Lindner, J. R. *Nat. Rev. Drug Discovery* **2004**, *3*, 527−532. (b) Emerich, D. F.; Thanos, C. G. *Expert Opin. Biol. Ther.* **2003**, *3*, 655−663.

(6) (a) Percec, V.; Wilson, D. A.; Leowanawat, P.; Wilson, C. J.; Hughes, A. D.; Kaucher, M. S.; Hammer, D.; ALevine, D. H.; Kim, A. J.; Bates, F. S.; Davis, K. P.; Lodge, T. P.; Klein, M. L.; DeVane, R. H.; Aqad, E.; Rosen, B. M.; Argintaru, A. O.; Sienkowska, M. J.; Rissanen, K.; Nummelin, S.; Ropponen, J. *Science* **2010**, *328*, 1009−1014. (b) Allen, T. M.; Cullis, P. R. *Science* **2004**, *303*, 1818−1821. (c) Langer, R. *Nature* **1998**, *392*, 5−10.

(7) (a) Foster, E. J.; Berda, E. B.; Meijer, E. W. *Macromolecules* **2010**, *43*, 1430−1437. (b) Foster, E. J.; Berda, E. B.; Meijer, E. W. *J. Am. Chem. Soc.* **2009**, *131*, 6964−6966. (c) Hamilton, S. K.; Harth, E. *ACS Nano* **2009**, *3*, 402−410. (d) Beck, J. B.; Killops, K. L.; Kag, T.; Sivanandan, K.; Bayles, A.; Mackay, M. E.; Wooley, K. L.; Hawker, C. J. *Macromolecules* **2009**, *42*, 5629−5635. (e) Adkins, C. T.; Muchalski, H.; Harth, E. *Macromolecules* **2009**, *42*, 5786−5792.

(8) (a) Chaudhuri, R. G.; Paria, S. *Chem. Rev.* **2012**, *112*, 2373−2433. (b) *Polymer-Based Nanostructures. Medical Applications*; Broz, P., Ed.; RCS Publishing: Cambridge, 2010. (c) Mason, B. P. ; Steinbacher, J. L.; McQuade, D. T. *Polymeric Capsules: Catalysis and Drug Delivery in Molecular Recognition and Polymers*; Rotello, V., Thayumanavan, S.), Eds.; Wiley: Hoboken, NJ, 2008; Chapter 8, pp 179−206.

(9) (a) Maeda, K.; Wakasone, S.; Shimomura, K.; Ikai, T.; Kanoh, S. *Chem. Commun.* **2012**, *48*, 3342−3344. (b) Tang, Z.; Iida, H.; Hu, H.-Y.; Yashima, E. *ACS Macro Lett.* **2012**, *1*, 261−265. (c) Ohsawa, S.; Sakurai, S.-I.; Nagai, K.; Maeda, K.; Kumaki, J.; Yashima, E. *Polym. J.* **2012**, *44*, 42−50. (d) Maeda, K.; Muto, M.; Sato, T.; Yashima, E. *Macromolecules* **2011**, *44*, 8343−8349. (e) Miyake, G. M.; Iida, H.; Hu, H.-Y.; Tang, Z.; Chen, E. Y.-X.; Yashima, E. *J. Polym. Sci. Part A: Polym. Chem.* **2011**, *49*, 5192−5198. (f) Schwartz, E.; Koepf, M.; Kitto, H. J.; Nolte, R. J. M.; Rowan, A. E. *Polym. Chem.* **2011**, *2*, 33−47. (g) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 1430−1433. (h) Yashima, E.; Maeda, K.; Lida, H.; Furusho, Y.; Nagai, K. *Chem. Rev.* **2009**, *109*, 6102−6211. (i) Liu, J.; Lam, J. W. Y.; Tang, B. Z. *Chem. Rev.* **2009**, *109*, 5799−5867. (j) Rosen, B. M.; Wilson, C. J.; Wilson, D. A.; Peterca, M.; Imam, M. R.; Percec, V. *Chem. Rev.* **2009**, *109*, 6275−6540. (k) Sierra, T. *Expresion of Chirality in Polymers in Chirality at the Nanoscale: Nanoparticles, Surfaces Materials and More*; Amabilino, D. B., Ed.; Wiley-VCH, Weiheim, 2009; Chapter 5, pp 115−190. (l) Yashima, E.; Maeda, K.; Furusho, Y. *Acc. Chem. Res.* **2008**, *41*, 1166−1180. (m) Rudick, J. G.; Percec, V. *Acc. Chem. Res.* **2008**, *41*, 1641−1652.

(n) Yashima, E.; Maeda, K. *Macromolecules* **2008**, *41*, 3−12. (o) Yashima, E.; Maeda, K. *Helically Folding Polymers in Foldamers: Structure Properties and Applications*; Hecht, S.; Huc, I., Eds.; Wiley-VCH, Weiheim, 2007; Chapter 11, pp 331−366. (p) Maeda, K.; Yashima, E. *Top. Curr. Chem.* **2006**, *265*, 47−88. (q) Nakako, H.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **1999**, *32*, 2861−2864. (r) Tabata, M.; Tanaka, Y.; Sadahiro, Y.; Sone, T.; Yokota, K.; Miura, I. *Macromolecules* **1997**, *30*, 5200−5204.

(10) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11692−11696.

(11) Simionescu, C. I.; Percec, V.; Dumitrescu, S. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 2497−2509.

(12) Poly-**1** and poly-**2** were synthetized from the corresponding monomers with $[\mathrm{Rh(nbd)Cl}]_2$ as catalyst. The polymeric materials obtained showed a high cis content, as shown by the chemical shifts of the vinyl protons (5.7−5.8 ppm) and Raman resonances (1567, 1340, 1003 cm^{-1}). The molecular weight (M_n) of poly-**1** and poly-**2** was estimated to be 138 270, $M_w/M_n = 1.22$, and 96 415, $M_w/M_n = 1.36$, respectively, by SEC. See full details in ref 10.

(13) DLS analysis confirmed that the sizes obtained in solution match the sizes observed by microscopy.

(14) The amount of salt needed to induce a significant change of the helix sense is characteristic of the metal used (i.e., Ca^{2+}, less than 1 mol per mol mru; Ba^{2+}, more than 2 mol per mol mru).

(15) To produce helix induction, the addition of monovalent cations in THF is not practical because large M^+/mru ratios are needed (i.e., M^+/mru ≈ 15 mol/mol).

(16) It is known that a number of factors govern the metal coordination number (CN) in metal complexes and that all metal cations present several CNs. See: Dudev, M.; Wang, J.; Dudev, T.; Lim, C. *J. Phys. Chem. B* **2006**, *110*, 1889−1895.

(17) From the estimated molecular weights of poly-**1** and poly-**2** shown in ref 12, lengths of ≈522 nm (174 turns) and ≈363 nm (121 turns) can be calculated, respectively, giving (a) the molecular weight of a mru (265.11), which implies ≈521 mru for poly-**1** and ≈363 mru for poly-**2** and (b) 3 mru per turn and 3 nm pitch length, taken from the theoretical calculations (see ref 10).