

This is the peer reviewed version of the following article: Rodríguez, R., Arias, S.; Quiñoá, E.; Riguera, R.; Freire, F.. The role of the secondary structure of helical poly(phenylacetylene)s in the formation of nanoparticles from polymer-metal complexes (HPMCs). *Nanoscale*, 2017,9, 17752-17757. This article may be used for noncommercial purposes in accordance with RSC Terms and Conditions for self-archiving

Full Paper

The role of the secondary structure of helical poly(phenylacetylene)s in the formation of nanoparticles from polymer-metal complexes (HPMCs)

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Rafael Rodríguez[‡], Sandra Arias[‡], Emilio Quiñoá, Ricardo Riguera* and Félix Freire*

www.rsc.org/

The great importance of the secondary structure (compressed/stretched) of helical poly(phenylacetylene)s (PPAs) in the formation of nanostructures (nanospheres, nanotoroids) by complexation with metal ions of diverse valence is demonstrated. PPAs bearing the same chelating units [anilide of (*R*)-methoxyphenylacetic acid] but displaying different helical scaffolds show great differences in their nanostructuration due to the different secondary structure of their helices despite they complex mono- and divalent metal ions in analogous ways. This key 3-D structural feature has not been taken into account previously when studying the nanostructuration of helical polymer-metal complexes (HPMCs).

Introduction

The study of chirality at the nanoscale level has drawn the attention of many research groups because of the potential of the chiral materials that can be developed.¹ Chiral nanostructures (fibres, nanospheres, nanotubes) have been prepared from different types of building blocks that go from small molecules with self-assembly properties,² to dendrimers³ and polymers.⁴ Moreover, metal ions have been used as crosslinking agents to generate nanostructures, the shape and properties of which can be adjusted by changing the metal ion involved in the stabilization of the nanomaterial. Following this line of research, metal-organic frameworks (MOFs),⁵ metal-peptide complexes⁶ and polymer-metal complexes have been used to prepare these nanomaterials.

Results and Discussion

In our group, we have explored the use of helical polymer-metal complexes (HPMCs) derived from poly(phenylacetylene)s (PPAs) to prepare chiral nanostructures⁷ with tuneable helical sense by resorting to appropriate metal ions. For instance, a PPA [i.e., *p*-poly-(*R*)-1] bearing the anilide of (*R*)- α -methoxy- α -phenylacetic acid^{7b-c} — in the dual role of pendant and coordinating moiety—, can be made to adopt either the *M* or the *P* helical sense by complexation with monovalent^{7c} or divalent metal ions^{7b} respectively. Moreover, these helically oriented HPMC may be forced to aggregate spontaneously by adjusting the polymer/metal/cosolvent ratio, which activates the crosslinking ability of the metal ion that produces both the corresponding *M* or *P* helicities and the macroscopically chiral nanospheres. Interestingly, we found that while the helical sense induction ability of the metal ions was a general feature for a large series of mono and divalent ions, their aggregation capability was more limited. It works perfectly well with all the divalent metal ions tested (i.e., Ca²⁺, Ba²⁺, Mn²⁺, Zn²⁺, Co²⁺, Ni²⁺, Mg²⁺, Fe²⁺, Cu²⁺), generating *P* nanospheres with tuneable size, good stability and low polydispersion.^{7c} On the contrary, only Ag⁺ is able to trigger the aggregation process and produce *M* nanospheres^{7b} among different monovalent metal ions tested. For instance, ions such as Li⁺ and Na⁺ induce the expected single-handed *M* helix without controlling the aggregation process.^{7b} Thus, although both mono and divalent metal ions produce complexes (HPMCs) with precise structure and helical sense, their nanostructuration to form helical nanoparticles is apparently determined just by the type of metal ion. To sum up, aggregation is limited to divalent ions, being Ag⁺ the exception in the family of monovalent ions, probably due to its ionic size and coordination ability. It is known that, in MOFs, the organic building block plays an important role in their structure, being important to place the coordinating groups far away from each other in order to promote the growing of the framework.

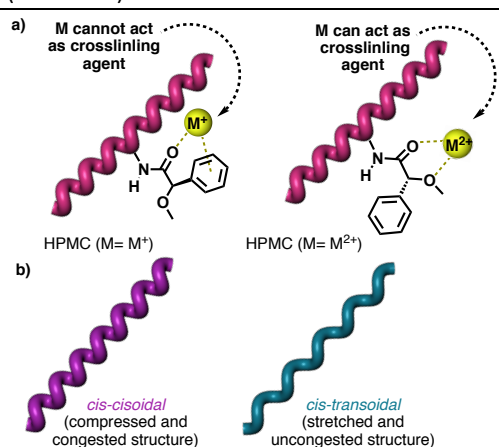
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain.
E-mail: felix.freire@usc.es, ricardo.riguera@usc.es

[‡] These authors contributed equally.

Electronic Supplementary Information (ESI) available: [Synthesis of monomers and polymers, thermal studies, IR measurements of different polymers, CD studies, aggregation studies, supporting references]. See DOI: 10.1039/x0xx00000x

In a similar approach we decided to study the role of the helical structure adopted by the HPMC in its nanostructuration. Thus, herein we will show that the different aggregation ability of the HPMCs is governed not only by the different chelation mode of mono and divalent ions, but also by the secondary structure of the HPMC chain—more or less compressed/extended helix—that plays a crucial role in the success of the aggregation.

Aggregation is an intermolecular process, and we reasoned that the location of the metal ion in the HPMC—more or less exposed to interlock different polymer chains—might be essential to explain those differences. Then, the location of the metal ion into the HPMCs should depend mainly on two factors: i) the coordination mode of the metal ion towards the pendant group and ii) the elongation degree of the helical scaffold (Scheme 1).



Scheme 1. Schematic representation of: (a) a PPA with different coordination modes towards mono- and divalent metal ions, and (b) two PPAs with different helical structure (*cis-cisoidal*, compressed and *cis-transoidal*, stretched).

p-poly-(*R*)-1/Mⁿ⁺ complexes with mono- and divalent metal ions show clear structural differences, based on the different coordination modes of those ions towards a *cis-cisoidal* helix (Scheme 1a). Thus, in the HPMCs of divalent ions, the metal chelates the carbonyl and methoxy group and fixes a *synperiplanar* (*sp*) conformation at the pendant moiety (Scheme 1a, Figure 1b).⁸ In this kind of HPMC, the metal is placed far away from the backbone. This fact facilitates its role as crosslinking agent and the formation of stable nanospheres, because it is independent of the “crowded” surroundings of the *cis-cisoidal* helix (Figure 1b).

On the contrary, in the HPMCs of monovalent metal ions, the metal coordinates the amide group and establishes a cation- π interaction with the aryl ring of the pendant group, which fixes the antiperiplanar (*ap*) conformation (Scheme 1a, Figure 1c). In this conformer, the metal ion is placed close to the backbone, being less exposed to the external part of the helix than in the case of HPMCs of divalent metal ions (Figure 1c). This location of the ion works against its crosslinking ability, and therefore the aggregation is limited, being not possible to control the formation of *p*-poly-(*R*)-1 nanospheres with monovalent metal ions.^{7c}

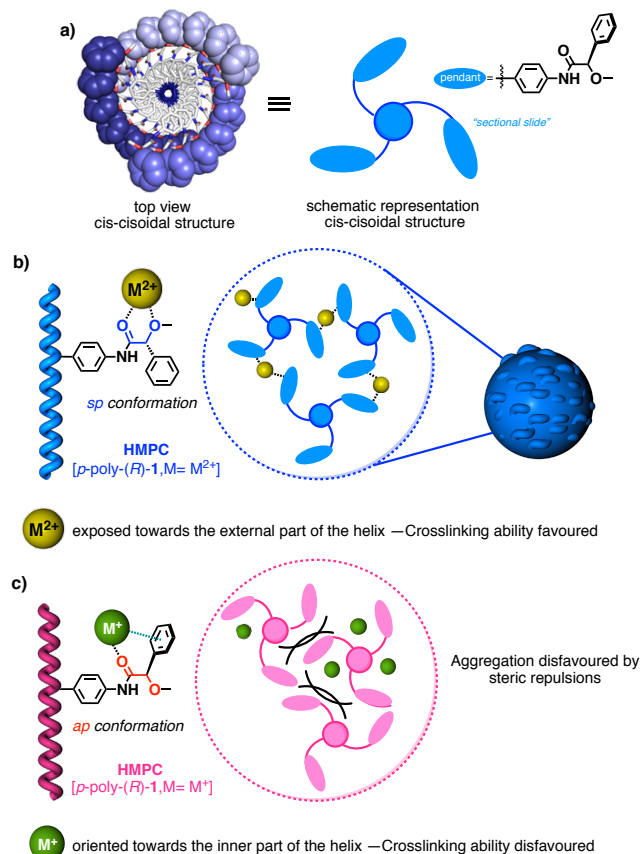
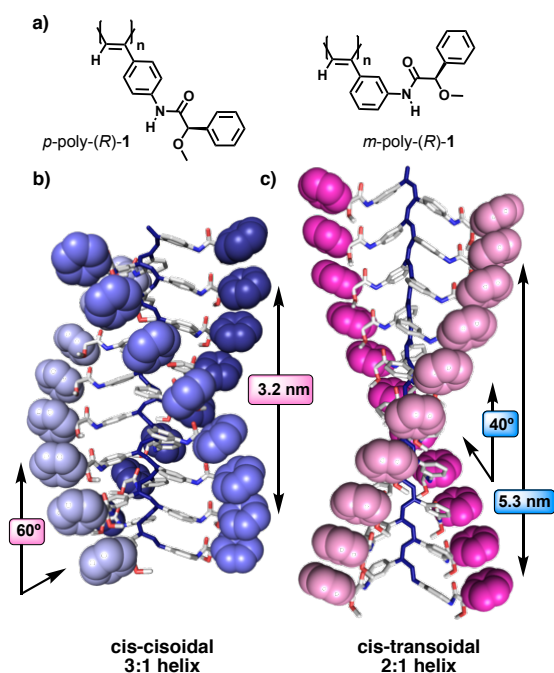


Figure 1. a) Top view of the *cis-cisoidal* structure for *p*-poly-(*R*)-1 and its schematic representation. b) Structure of the *p*-poly-(*R*)-1/M²⁺ complex and conceptual representation showing its crosslinking ability. c) Structure of the *p*-poly-(*R*)-1/M⁺ complex and conceptual representation showing a disfavoured aggregation process.

As a result, the crosslinking ability of HPMCs possessing *cis-cisoidal* helices is exclusively determined by the structure of the complexes formed at the pendants, where the location of the metal ion is essential to form low polydisperse nanospheres.

In order to demonstrate this hypothesis, we decided to study these two factors—coordination mode and helical scaffold—in deep. Thus, we carried out a comparison of the HPMC structure and the aggregation behaviour of two PPAs that bear the same chelating unit—i.e., the anilide of (*R*)- α -methoxy- α -phenylacetic acid—linked to the polymeric backbone through the *para* [i.e., *p*-poly-(*R*)-1] and *meta* [i.e., *m*-poly-(*R*)-1] positions respectively. Both polymers show different helical scaffold^{8,9} (Scheme 2a): *p*-poly-(*R*)-1, adopts a compressed *cis-cisoidal* helix (3 residues per turn, Scheme 2b),⁸ while *m*-poly-(*R*)-1 exists as an equilibrium between *cis-cisoidal* (3 residues per turn, Scheme 2b) and *cis-transoidal* (more stretched, 2 residues per turn, Scheme 2c) helices (Figure 2a).⁹



Scheme 2. a) Chemical structures of *p*-poly-(*R*)-MPA and *m*-poly-(*R*)-MPA. b) *Cis-cisoidal* (3 residues per turn) and (c) *cis-transoidal* (2 residues per turn) helical structures adopted by poly-*m*-(*R*)-1.

Hence, to determine the importance of the helical scaffold in the formation of low polydisperse nanospheres, we performed a titration of the *meta*-polymer —*m*-poly-(*R*)-1, 0.3 mg/mL in chloroform— with different amounts of LiClO₄ (10 mg/mL in THF). The amplification of the left-handed helix was observed (Figure 2c) by formation of a HPMC with a coordinated structure similar to the one described before for the *p*-poly-(*R*)-1/Li⁺ complex: coordination of Li⁺ to both amide and phenyl groups of the MPA moiety (the latter coordination by cation- π interaction), which fix the *ap* conformation at the pendant (Figure 2b).^{10b}

Moreover, during these studies a red shift was observed on the UV spectrum of the polyene backbone indicating that the equilibrium between the two helices adopted by *m*-poly-(*R*)-1 (*cis-cisoidal*/*cis-transoidal*, Figure 2a) is being shifted towards the stretched one (i.e., *cis-transoidal* helix) upon complexation with monovalent metal ions (Figure 2b-d).¹² Similar results were obtained for other *m*-poly-(*R*)-1/M⁺ complexes (M⁺= Na⁺ and Ag⁺; see ESI).

This structural change in *m*-poly-(*R*)-1 (the increase of the *cis-transoidal* population) is the best scenario to study the aggregation of the *m*-poly-(*R*)-1/Li⁺ complex, assuming that the helical structure of the polymer plays an important role in the nanosphere formation from HPMCs. As we mention before, in this *cis-transoidal* structure the metal ion is placed in an outer part of the helix and is more prone to act as crosslinking agent (Figure 3).

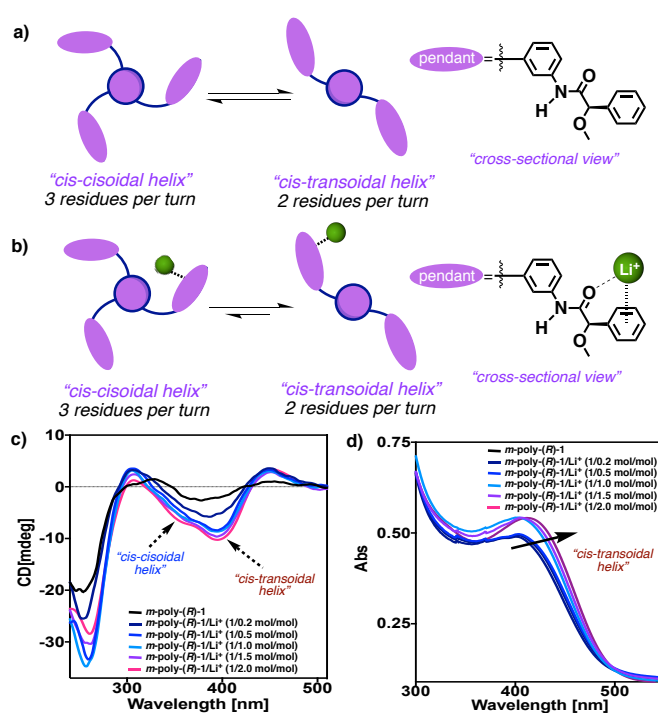


Figure 2 Schematic representation of the equilibrium between a compressed *cis-cisoidal* and a stretched *cis-transoidal* helical structure adopted by *m*-poly-(*R*)-1 (a) before and (b) after the addition of LiClO₄. c) CD and (d) UV spectra showing an increase in the population of the *cis-transoidal* helix once LiClO₄ is added to *m*-poly-(*R*)-1 solution. [*m*-poly-(*R*)-1]=0.3 mg/mL CHCl₃; [LiClO₄]= 10 mg/mL THF.

Interestingly, and in accordance with our hypothesis, the *m*-poly-(*R*)-1/Li⁺ complex suffered spontaneous aggregation forming left-handed nanospheres (Figure 4).

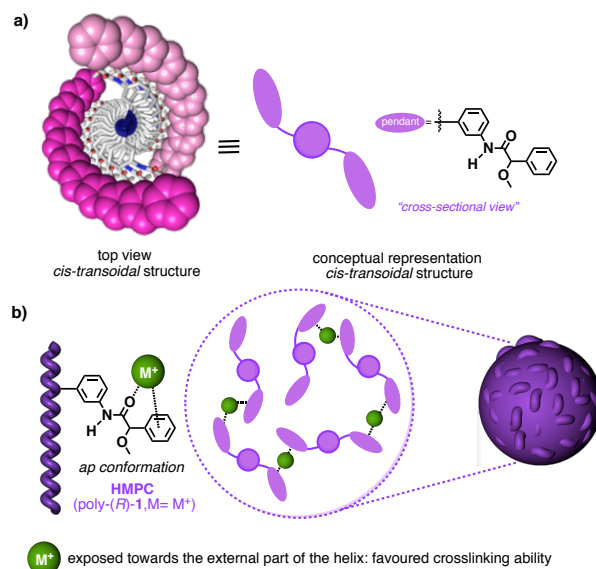


Figure 3 a) Top view of the *cis-transoidal* structure for *m*-poly-(*R*)-1 and its schematic representation. B) Structure of the *m*-poly-(*R*)-1/M⁺ complex and scheme showing its potential crosslinking ability.

Thus, a *m*-poly-(*R*)-1/Li⁺ complex solution at 1/0.5 mol(mru)/mol ratio, showed by DLS stable and low polydisperse nanospheres (46 nm diameter, PDI= 0.105; Figure 4) with *M* chirality (CD negative at the vinylic region) and with tuneable size by changing the polymer/metal ratio (Figure 4a).

Electron microscopy studies (SEM) corroborated these results showing the presence of nanospheres in the solid state (Figures 4b-c). Analogous studies with Na^+ and Ag^+ showed also the formation of chiral nanospheres, confirming that to control the aggregation of the HPMCs with monovalent ions, the presence of a stretched helical structure is required (see ESI).

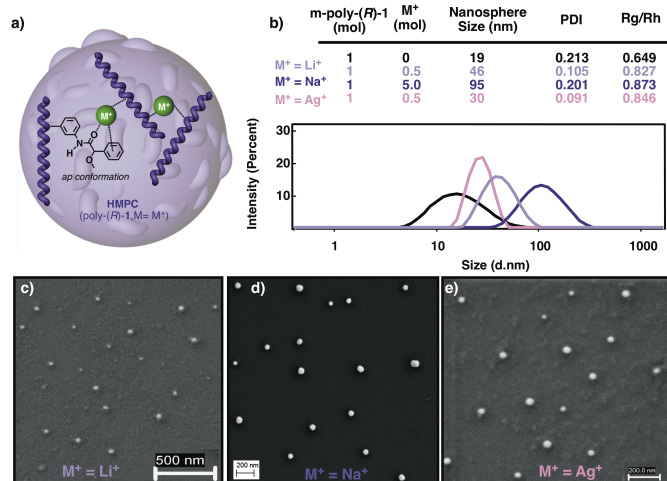


Figure 4. a) Schematic illustration of the aggregation process of *m*-poly-(*R*)-1 with monovalent metal ions to generate chiral nanospheres b) DLS studies of a *m*-poly-(*R*)-1/ M^+ complex ($M^+ = \text{Li}^+$, Na^+ and Ag^+). SEM studies of c) *m*-poly-(*R*)-1/ Li^+ , d) *m*-poly-(*R*)-1/ Na^+ and e) *m*-poly-(*R*)-1/ Ag^+ in a 1/0.5 mol/mol ratio, [*m*-poly-(*R*)-1] = 0.3 mg/mL CHCl_3 ; [LiClO_4] = 10 mg/mL MeOH.

In order to further confirm the original hypothesis, the aggregation studies were also performed using divalent metal ions such as Ca^{2+} or Ba^{2+} . First, we checked the coordination of the metal to the polymer and the presence/absence of helical induction or helical inversion. The results obtained showed that the divalent metal ions coordinate only to the carbonyl group (as inferred from IR experiments, see ESI), without inducing any helical change on the PPA (Figure 5). DLS experiments of *m*-poly-(*R*)-1/ Ba^{2+} complex solution at 1/0.5 mol/mol ratio showed the formation of stable and low polydisperse nanospheres (46 nm diameter, PDI = 0.056; Figure 5c). Moreover, during the drop-casting and drying process, the aggregation generated toroidal nanostructures with *M* chirality (negative CD at the vinylic region; Figure 5d and ESI). See also ESI for HPMC ($M = \text{Ca}^{2+}$) studies.

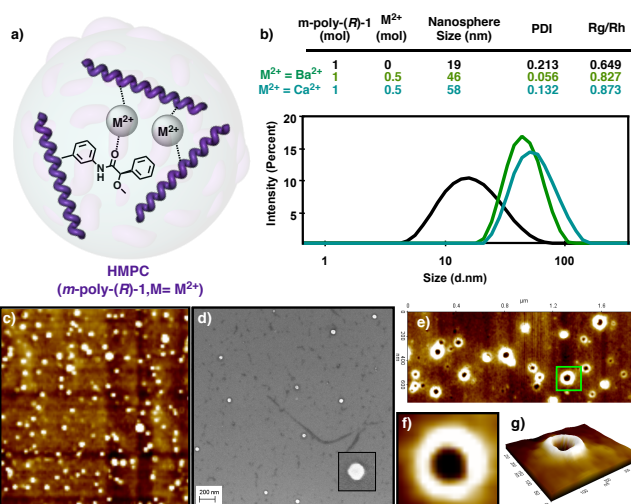


Figure 5. a) Schematic illustration of the aggregation process of *m*-poly-(*R*)-1 with divalent metal ions to generate chiral nanospheres b) DLS studies of a *m*-poly-(*R*)-1/ M^{2+} complex ($M^{2+} = \text{Ba}^{2+}$ and Ca^{2+}). c) AFM studies of *m*-poly-(*R*)-1/ Ba^{2+} complex. d) SEM studies of *m*-poly-(*R*)-1/ Ba^{2+} complex. e) AFM studies of *m*-poly-(*R*)-1/ Ba^{2+} complex showing toroidal structures. f) Magnification of the highlighted area in the previous image. g) 3D-projection of image f).

Conclusions

In summary, we have demonstrated that the aggregation of HPMCs is determined by both coordination mode of the metal ion to the pendant group and elongation of the polyene skeleton. Thus, while divalent metal ions chelate the *p*-poly-(*R*)-1 in such a way that the metal ion is exposed and prone to act as crosslinking agent, in the case of *p*-poly-(*R*)-1/ M^+ complexes the metal ion is placed in an inner part of the helix and close to the polyene backbone. This structural situation disrupts the crosslinking ability of the monovalent metal ion. In addition, if the elongation of the polyene backbone is modified, the crosslinking ability of the monovalent metal ions can be reactivated. Thus, in a more extended helical structure —*m*-poly-(*R*)-1— that bears the same MPA pendant moiety as *p*-poly-(*R*)-1, monovalent metal ions such as Li^+ , Na^+ and Ag^+ can act as crosslinking agents, producing low polydisperse nanospheres by chelating the same functional groups at the pendant than in the case of *p*-poly-(*R*)-1/ M^+ . Moreover, the divalent ions —e.g., Ca^{2+} or Ba^{2+} — show a similar coordination mode to the carbonyl group as in the case of monovalent ions, forming nanospheres with controlled size and low polydispersity. Furthermore, these nanospheres can collapse during the drop-casting and drying process, generating chiral toroids. In the case of *m*-poly-(*R*)-1, the metal ion (M^+ or M^{2+}) is always placed in the external part of the helix. These results indicate that both chelation and secondary structure play a key role in the aggregation process of HPMCs and hence the two factors must be taken into account when designing new HPMC nanostructures.

Acknowledgements

We thank Ministerio de Economía y Competitividad [CTQ2015-70519-P, CTQ2014-61470-EXP], FPI (R. Rodríguez), Fundación Gil Dávila (S. Arias), Xunta de Galicia (Centro singular de investigación de Galicia accreditation 2016-2019, GRC2014/040) and European Union (European Regional Development Fund - ERDF) for financial support.

Notes and references

- For reviews on supramolecular chirality see: (a) F. Freire, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2016, **116**, 1242; (b) M. Liu, L. Zhang and T. Wang, *Chem. Rev.*, 2015, **115**, 7304; (c) L. Zhang, L. Qin, X. Wang, H. Cao and M. Liu, *Adv. Mater.*, 2014, **26**, 6959; (d) Y. Yang, Y. Zhang and Z. Wei, *Adv. Mater.*, 2013, **25**, 6039; (e) Y. Wang, J. Xu, Y. Wang and H. Chen, *Chem. Soc. Rev.*, 2013, **42**, 2930; (f) H. Miyake and H. Tsukube, *Chem. Soc. Rev.*, 2012, **41**, 6977; (g) D. K. Smith, *Chem. Soc. Rev.*, 2009, **38**, 684.
- (a) C. Ren, J. Zhang, M. Chen and Z. Yang, *Chem. Soc. Rev.*, 2014, **43**, 7257; (b) Z. Huang, S.-K. Kang and M. Lee, *J. Mater. Chem.*, 2011, **21**, 15327; (c) I. Danila, F. Riobó, F. Piron, J. Puigmartí-Luis, J. D. Wallis, M. Linares, H. Gren, D. Beljonne, D. B. Amabilino and N. Avarvari, *J. Am. Chem. Soc.*, 2011, **133**, 8344; (d) V. Percec, D. A. Wilson, P. Leowanawat, C. J. Wilson, A. D. Hughes, M. S. Kaucher, D. A. Hammer, D. H. Levine, A. J. Kim, F. S. Bates, K. P. Davis, T. P. Lodge, M. L. Klein, R. H. DeVane, E. Aqad, B. M. Rosen, A. O. Argintaru, M. J. Sienkowska, K. Rissanen, S. Nummelin and J. Ropponen, *Science*, 2010, **328**, 1009; (e) T. F. A. De Greef, M. M. J. Smulders, M. Wolffs, A. P. H. J. Schenning, R. P. Sijbesma and E. W. Meijer, *Chem. Rev.*, 2009, **109**, 5687.
- (a) B. M. Rosen, C. J. Wilson, D. A. Wilson, M. Peterca, M. R. Imam and V. Percec, *Chem. Rev.*, 2009, **109**, 6275; (b) V. Percec, M. R. Imam, M. Peterca, D. A. Wilson, R. Graf, H. Spiess, V. S. K. Balagurusamy and P. A. Heiney, *J. Am. Chem. Soc.*, 2009, **131**, 7662; (c) V. Percec, M. R. Imam, M. Peterca, D. A. Wilson and P. A. Heiney, *J. Am. Chem. Soc.*, 2009, **131**, 1294; (d) V. Percec, M. Peterca, A. E. Dulcey, M. R. Imam, S. D. Hudson, S. Nummelin, P. Adelman and P. A. Heiney, *J. Am. Chem. Soc.*, 2008, **130**, 13079.
- (a) J. Lin, H. Huang, M. Wang and J. Deng, *Polym. Chem.*, 2016, **7**, 1675; (b) B. Zhao, J. Deng and J. Deng, *Macromol. Rapid Commun.*, 2016, **37**, 568; (c) D. Liu, Y. Li, J. Deng and W. Yang, *Polymer*, 2014, **55**, 840; (d) W. Li, H. Huang, Y. Li and J. Deng, *Polym. Chem.*, 2014, **5**, 1107; (e) C. Song, X. Liu, D. Liu, C. Ren, W. Yang and J. Deng, *Macromol. Rapid Commun.*, 2013, **34**, 1426; (f) V. Percec, A. E. Dulcey, V. S. K. Balagurusamy, Y. Miura, J. Smidrkal, M. Peterca, S. Nummelin, U. Edlund, S. D. Hudson, P. A. Heiney, H. Duan, S. N. Magnov and S. S. Vinogradov, *Nature*, 2004, **430**, 764.
- (a) Q. –Zhu and Q. Xu, *Chem. Soc. Rev.* 2014, **43**, 5468; (b) H. Furukawa, K. E. Cordova, M. O. Keeffe and O. M. Yaghi, *Science*, 2013, **341**, 1230444; (c) A. Carnó-Sánchez, I. Imaz, M. Cano-Sarabia and D. MasPOCH, *Nat. Chem.*, 2013, **5**, 203; (d) L. E. Kreno, K. Leong, O. K. Farha, M. Allendorf, R. P. Van Duyne and J. T. Hupp, *Chem. Rev.*, 2012, **112**, 1105; (e) N. Stock and S. Biswas, *Chem. Rev.*, 2012, **112**, 933.
- (a) M. Rubio-Martínez, J. Puigmartí-Luis, I. Imaz, P. S. Dittrich and D. MasPOCH, *Small*, 2013, **9**, 4160; (b) E. Gazit, *Chem. Soc. Rev.*, 2007, **36**, 1263; (c) X. Fu, Y. Wang, L. Huang, Y. Sha, L. Gui, L. Lai and Y. Tang, *Adv. Mater.*, 2003, **15**, 902.
- (a) S. Arias, M. Núñez-Martínez, E. Quiñoá, R. Riguera and F. Freire, *Small*, 2017, **13**, 1602398. (b) S. Arias, F. Freire, E. Quiñoá and R. Riguera, *Angew. Chem. Int. Ed.*, 2014, **53**, 13720; (c) F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *J. Am. Chem. Soc.*, 2012, **134**, 19374.
- (a) R. Rodríguez, J. Ignés-Mullol, F. Sagués, E. Quiñoá, R. Riguera and F. Freire, *Nanoscale*, 2016, **8**, 3362; (b) F. Freire, J. M. Seco, E. Quiñoá, R. Riguera, *Angew. Chem. Int. Ed.*, 2011, **50**, 11692.
- (a) R. Rodríguez, E. Quiñoá, R. Riguera and F. Freire, *J. Am. Chem. Soc.*, 2016, **138**, 9620-9628. (b) F. Freire, E. Quiñoá, R. Riguera, *Chem. Commun.* 2017, **53**, 481-492.
- (a) S. Arias, J. Bergueiro, F. Freire, E. Quiñoá and R. Riguera, *Small*, 2016, **12**, 238; (b) S. Arias, F. Freire, E. Quiñoá, R. Riguera, *Polym. Chem.*, 2015, **6**, 4725. (c) J. Bergueiro, F. Freire, E. P. Wendler, J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Sci.*, 2014, **5**, 2170.
- Only *p*-poly-(R)-1/Ag⁺, from all the different HPMCs of monovalent metal ions tested, produces stable and low polydisperse nanospheres. This fact that can be explained due to the different size and coordination ability of Ag⁺.
- VT-CD measurements of the *m*-poly-(R)-1/Li⁺ complex indicate a higher population of the stretched helix when the temperature increases (See ESI).

Nanoscale

Full Paper

TOC

The secondary structure of chiral helical polymers —forming helical polymer-metal complexes (HPMCs) in coordination with metal ions— plays a major role in their subsequent nanostructuration generating nanostructures, such as nanospheres and nanotoroids, constituted by chiral materials.

