Chiro-Thermoresponsive Helical Elastin-Based Side-Chain Poly(phenylacetylene)s

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ABSTRACT: The thermoresponsive behaviour of an elastin based polymer can be altered by the polymeric macromolecular conformation. Thus, when the elastin basic amino-acid sequence VPGVG (V = Valine, P = Proline, G = Glycine) is used as a pendant group of a poly(phenylacetylene) (PPA) its thermoresponsive behavior can be remotely detected due to conformational changes on the formed helix. Circular dichroism (CD) experiments at different temperatures show an inversion of the first Cotton effect (450 nm) at 27 ºC (T_{ICD}) that matches with the cloud point temperature (T_{CP}) obtained by turbidimetric analysis. Interestingly, this elastin-based side-chain poly(phenylacetylene) (EBPPA) shows an upper critical solution temperature (USCT), not expected by design with elastin based polymers. In addition, the EBPPA shows a low pH and concentration dependency of its thermoresponsive properties, which is uncommon for elastin-based or UCST polymers. All these results indicate that the macromolecular structure like a helical one has a strong influence on its thermoresponsive response and tunes its native behavior. Finally, it was found that the polymer self-assembles into spherical nanoparticles with hydrodynamic diameters of 140 nm at the hydrophobic state.

The ability of some macromolecules to respond to temperature, which is termed thermoresponsiveness, constitutes the basis for a number of responsive systems being studied

and applied nowadays in several pertinent fields.[1] Taking advantage of their thermal properties, these macromolecules can be employed to form different smart materials with novel properties like mechanical hysteresis,[2] triggered drug delivery,[3] cell banking,[4] permittivity switching,[5] and sensing[6] among others. The most applied thermoresponsive phenomenon is mainly based on a temperature driven hydropathic change in the macromolecules. This hydropathic transition in water can occur either from a hydrophilic to a hydrophobic state of the macromolecule or *vice versa* upon an increase in temperature, showing a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST) respectively. There are a vast number of LCST polymers that have been reported with transition temperatures at biological relevant temperatures, but conversely, the number of UCST polymers working at these temperatures is limited. This limitation arises due to the fact that the hydrophobic to hydrophilic transition is usually based on dynamic hydrogen bonds or zwitterionic interactions that are highly dependent on concentration, pH, and ionic strength.[7-9] To solve these drawbacks, different approaches for the tuning of the thermoresponsiveness of these materials were utilized, like control over the polymer size, co-polymerization with a more hydrophilic or hydrophobic monomer, and even polymer post-functionalization.[10] Nevertheless, all these strategies do not consider the macromolecular conformational effects on their design. Furthermore, they are not always able to modify the transition temperatures of UCST polymers to a biologically pertinent range.

Elastin is one of the most important families of natural structural proteins present in the extracellular matrix, providing different tissues with the required strength and flexibility.[11] In addition, elastin has a high biotechnological interest, not only for its mechanical and thermoresponsive properties, but also for its simple composition of a repeated amino-acid sequences that makes it easily accessible through protein engineering. The prominent amino acid sequence (VPGVG, V = Valine, P = Proline, G = Glycine) present in tropoelastin was found to be responsible for its thermally reversible phase transition at temperatures from 27 to 40 ºC.[12] Interestingly, the thermoresponsive properties of these proteins can be tailored by genetic engineering.[13-14] For instance, Chilkoti and García Quiroz demonstrated that varying or

adding key residues in the tropoelastin repeated sequence, its hydropathy can be tuned and therefore its LSCT behavior.[15]

Moreover, the elastin amino-acid basic sequence has been already employed as a monomer in atom-transfer radical-polymerization or reversible addition-fragmentation chain-transfer polymerization to achieve elastin-like side-chain based polymers (EBP) that maintain a LCST performance with strong concentration and pH dependency.[16-17] In these cases, the polymer backbone acts only as conector of the elastin-based side chains, providing them with enough flexibility to respond to the temperature changes in a simmilar manner to the natural elastine. Nevertheless, the control over the macromolecular structure in this kind of stimuli-responsive materials can be ideally driven by the polymeric backbone. By ordering the pendants through a defined three dimensional structure, the interpendant interactions could lead to a control of the macromolecule thermoresponsivity or even to new behaviours not achivable by polymers with no structural order.

Therefore, we decided to include elastin motifs as a pendant group on a dynamic helical polymer with enough macromolecular structural order but with sufficient flexibility to assure the changes on the elastin oligomer. As a result, we expected that these thermoresponsive changes could be transformed in helical structural changes of the polymer that could be easily tracked by circular dichroism (CD). In this sense, poly(phenylacetylene)s (PPAs) were chosen as the helical scaffolds to bear the elastin sequence as a pendant group since they perfectly fit all the previously mentioned requirements. PPAs can show chiral amplification, helix inversion, elongation or compression of the helical backbone by conformational changes of the pendant group.[18-23] Moreover, PPAs also show several advantageous properties like pendant tolerability and controlled supramolecular self-assembly.[24-28] In the last few years, some thermoresponsive pendant groups have been attached to PPAs, but surprisingly no chiral response could be observed due to temperature changes.[29]

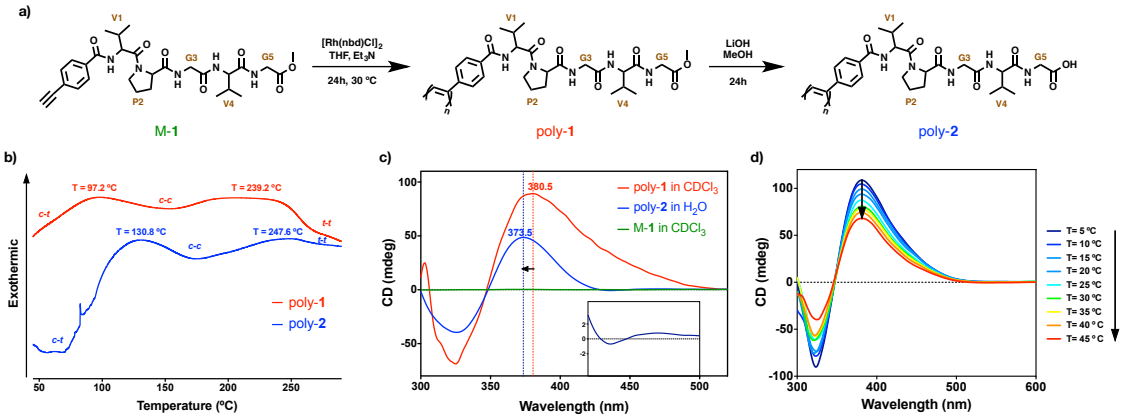

Figure 1. a) Synthetic scheme of poly-**1** and poly-**2**. b) DSC spectrum of the *cis-transoidal* protected polymer poly-**1** and deprotected poly-**2**. c) CD spectrum representation of poly-**1**, poly-**2**, and M-**1** at 25 ºC. d) VT-CD measurement of poly-**1** in $CDCl_3$ from 5 to 45 ºC at a concentration of 0.4 ∓mol/mL.

Herein we describe the synthesis and evaluation of an elastin-based side-chain helical poly(phenylacetylene) (EBPPA). More precisely, the pentamer VPGVG, the tropoelastin basic amino acid sequence was chosen as the elastin based derivative. This pentamer was attached to the 4-ethynilbenzoic acid through the *N*-terminus amine of the valine residue (**V1**) to generate the monomers *m*-PA-VPGVG-OMe (M-**1**) protected at the *C*-terminus with a methyl ester group (**Figure 1a**). Next, M-**1** was polymerized using the described [{Rh(nbd)Cl}$_2$] catalyzed methodology and afforded the protected EBPPA (poly-**1**) (**Figure 1a**).[30] Our design concerns itself with the reported thermoresponsive behavior in water of elastin-based side-chain polymers in a *C*-deprotected sequence.[31] Therefore, we performed the deprotection of poly-**1** with lithium hydroxide to yield poly-**2**, which showed a great solubility in water and phosphate-buffered saline solutions at different pHs. Poly-**1** and poly-**2** were fully characterized by nuclear magnetic resonance (NMR) and infrared and Raman spectroscopies (See **SI** for details). Due to the nature of the PPAs, matrix-assisted laser desorption/ionization – time of flight (MALDI-TOF) was not frequently used on their mass determination.[32] Notably, we found that the repeating unit of the EBPPA backbone could be obtained from the distribution of peaks in the MALDI-TOF spectra. Considering the monomer weight and the observed number of repeating units, the molecular weight distribution of the polymer could be attained. An average molar

mass (M_w) of 11799 Da with a narrow polydispersity index (PDI) of 1.06 was obtained, when sinapinic acid was used as a matrix (Supplementary **Figure S8**).

Differential scanning calorimetry (DSC) experiments showed a first peak at 90.7 and 130.8 ºC and a second peak at 239.2 and 247.6 ºC for poly-**1** and poly-**2**, respectively (**Figure 1b**). The first bands are characteristic of a backbone conformational change from *cis-transoidal* to *cis-cisoidal*, while the second bands can be attributed to a *cis-cisoidal* to *trans-transoidal* transformation. Therefore, the presence of a *cis-transoidal* polyene skeleton could be confirmed in both polymers.[33]

CD spectra of poly-**1** (0.4 ∓mol/mL, 25 ºC) showed a CD trace with 3 alternating positive and negative bands, which indicated the presence of a right-handed (*P*) helical structure (first positive Cotton effect) in chloroform (**Figure 1c**). On the other hand, the water CD spectra of poly-**2** at the same concentration and temperature revealed structural changes when compared to poly-**1** dissolved in chloroform. A new band at 450 nm was observed, while the rest of the spectra is similar to the one obtained for poly-**1**. El zoom de la fig no se vé parece que hay una primera positive banda a 500, en vez de ser la negative a 400 This new band is related to the PPA backbone that can be attributed to a rotation of the aryl ring to the polyene skeleton. The CD band related to the polyene skeleton at 380 nm showed a positive band, similar to the one obtained for poly-**1**, which indicated that poly-**2** therefore also had a right handed helical structure (positive Cotton effect).

Variable temperature (VT) CD experiments of poly-**1** showed the expected temperature dependent behavior of a PPA. The induced helical structure was more stable at lower temperatures than at higher ones, where the screw-sense excess decreased considerably (**Figure 1d**).[34-35]

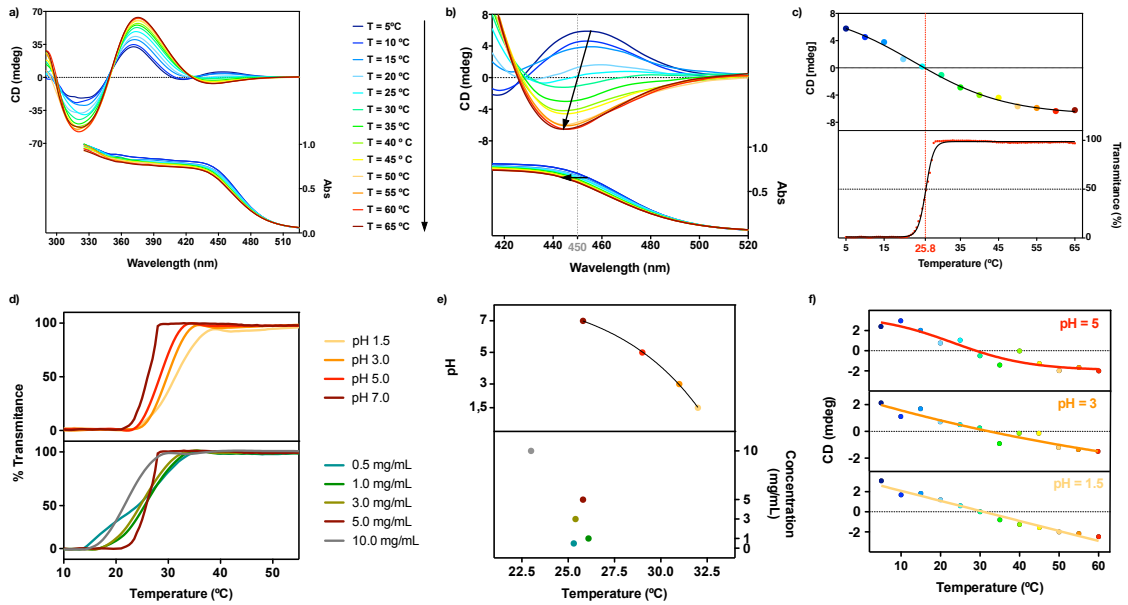

Figure 2. a) CD and UV-Vis spectra of poly-**2** in water (5 mg/mL) at different temperatures and b) its zoomed area from 410 until 520 nm. c) CD intensity values of poly-**2** at 450 nm showing the Cotton effect inversion of poly-**2** when increasing the temperature compared to its turbidimetric measurement represented in a normalized transmittance. d, e) pH and concentration dependency of poly-**2** transition temperature by turbidimety and f) its correlation with the CD inversion temperature at 450 nm.

VT-CD experiments were also performed for poly-**2** (0.4 ∓mol/mL H_2O) in a temperature range from 5 to 65 ºC. Interestingly, an inversion of the first Cotton effect (430-500 nm region) was observed when the temperature increased (**Figure 2a-b**). VT-CD values at 450 nm were represented and fitted to a sigmoidal equation. This fitting shows that the signal inversion (null CD intensity) takes place at a temperature of 25.8 ºC (T_{ICD}). Moreover, heating and cooling experiments revealed that this process was fully reversible, where the T_{ICD} remained constant in the different heating/cooling cycles (Supplementary **Figure S12**).

Remarkable results were obtained when turbidimetric measurements of poly-**2** at the same concentration and temperature range were carried out. It was found that the cloud point temperature corresponded to the temperature where the first Cotton effect was inverted (T_{ICD} = T_{CP}) (**Figure 2c**). Even more interestingly, we also found that this sharp transition took place in the EBPPA from a hydrophobic state at low temperatures to a hydrophilic one at temperatures above the T_{ICD}. This transition corresponded to a UCST polymer and opposed to the typical

LCST thermoresponsive behavior reported for EBPs, which indicated that the helical structure adopted by the polyphenylacetylene skeleton had a strong influence in the thermoresponsive behavior of the EBPPA.

Variable temperature ultraviolet-visible (VT-UV-Vis) studies also indicate that the EBPPA suffered a structural change at the T_{ICD}. A hypsochromic shift was observed at temperatures higher than the T_{ICD}, which indicated the presence of a more compressed helical structure above the transition temperature (**Figure 2a-b**). Moreover, it was found that the CD bands at 380 and 320 nm increased when the temperature rose, although the band at 450 nm was inverted. These results suggested a conformational change of the pendant group that was related with the stabilization of a compressed right-handed helix,[36] which demonstrated once more that the conformational changes on the pendant and then the hydropathic behavior of the EBPPA were directly related to the helical structure adopted by the PPA.

Then the pH dependence of the polymer thermoresponsivity was studied. Different pH values from neutral to acid (7, 5, 3, and 1.5) were screened to check the possible effect of the protonation of the terminal glycine residue. From these experiments, we found that the EBPPA showed the same UCST behavior for all the analyzed range of pH (**Figure 2d** and **e**), although the T_{CP} value slightly increased as pH decreased (from 26 to 33 ºC). This observation was in agreement with the corresponding T_{ICD} values obtained from CD experiments at those pHs (**Figure 2f** and Supplementary **Figure S13-16**). Turbidimetry of poly-**2** was also investigated at different concentrations (0.5 - 10.0 mg/mL), which showed almost no concentration dependency until 5 mg/mL (**Figure 2d, e**) except for a concentration of 10 mg/mL, where the T_{CP} value decreased around 3 ºC. These results clearly contrasted with the previously reported high pH and concentration dependency of other EBPs, which corroborated again the strong influence of the PPA helical structure on the thermoresponsive behavior of the EB side chain.[14]

It is known that the thermoresponsive behavior of the tropoelastin amino acid sequence $(VPGVG)_n$ in water undergoes a LSCT transition from a random coil to a β-spiral structure when heated. Through this process, the solvated water from the hydrophobic valines is spelled

and stabilized inside the entropically less favored and hydrophobic β-spiral. The same transition was also observed in short elastin-like peptides that showed a transformation from an expanded β-spiral type II form favored at low temperatures to a contracted form at temperatures above the transition.[20] On the contrary, although our EBPPA had the tropoelastin VPGVG sequence, its behavior was completely opposite to the parent peptide. Taking into account the conformation adopted by the VPGVG sequence in the hydrophobic and the hydrophilic states and our structural studies on the polyene backbone for poly-**2** (DSC, CD and UV), we could model the two possible helical structures adopted by EBPPA below and above the T_{CP} = 25.8 ºC (**Figure 3**).

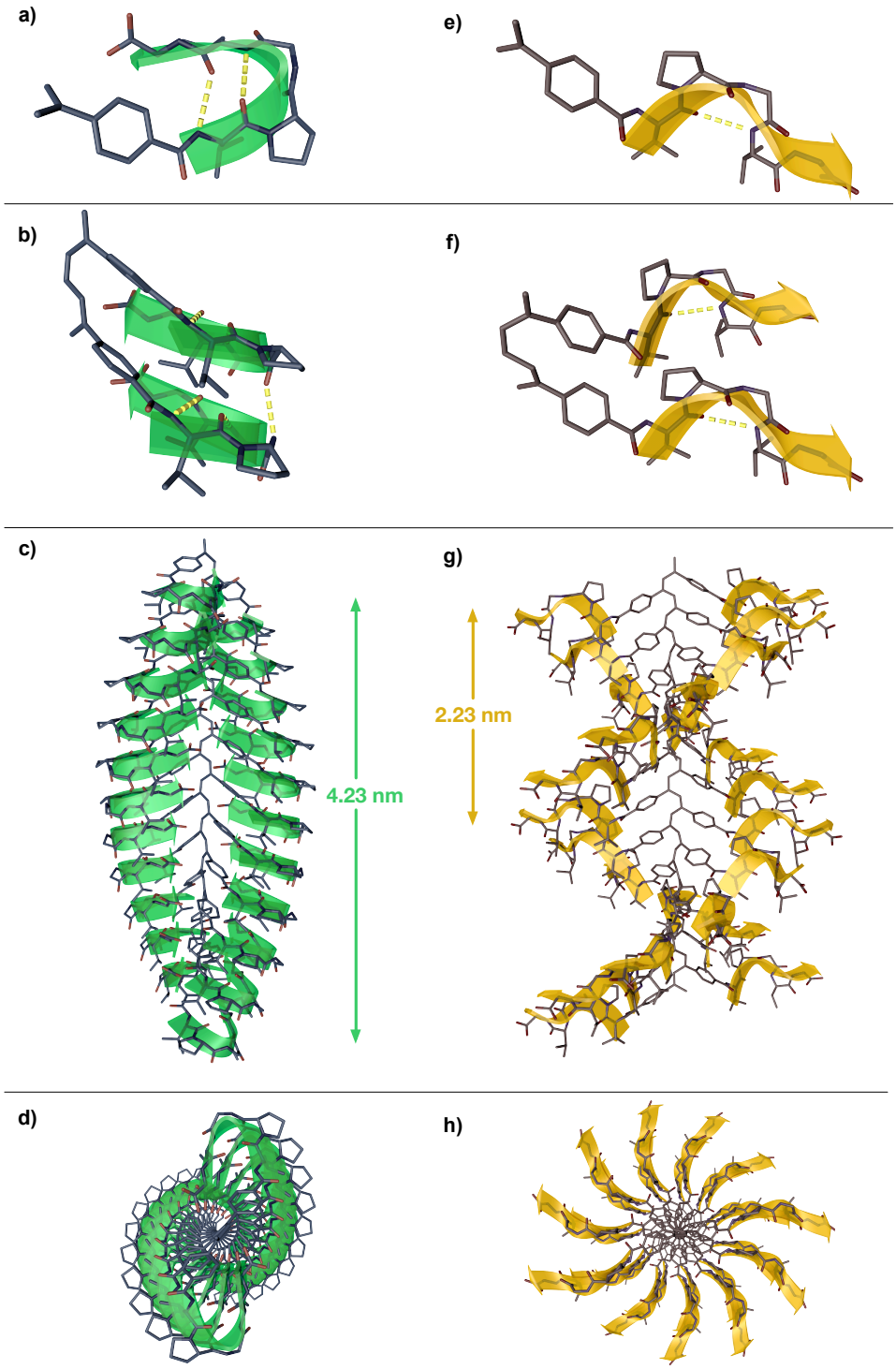

Figure 3. 3D-structural representations at the hydrophobic (below T_{ICD}, left side) and hydrophilic (above T_{ICD}, right side) state of: a,e) the monomers, b,f) two neighbouring pendants within the same helical side highlighting the possible inter- and intrapendant hydrogen bonds, c,g) lateral, and d,h) zenithal view of the proposed helical structures.

Below the T_{CP}, poly-**2** present a hydrophobic state, where the peptide pendant adopts a contracted β-spiral conformation that produces a stretching of the polyene scaffold to release the steric constrain produced by the compact peptide form. In this conformation, two intrapendant hydrogen bonds (**V1** N-H□□□O=C **V4**, **V1** C=O□□□HN **V4**) stabilize the β-spiral conformation, (**Figure 3a**) while an additional interpendant hydrogen bond stabilizes the helical scaffold (upper pendant **P2** C=O□□□H-N **G3** lower pendant) (**Figure 3b**). This fact results in an elongated structure, where the helical pitch is large enough to accommodate the contracted peptide chain in the helical groove (**Figure 3c, d**). The free carboxylic moieties are placed into the groove on this configuration and therefore the hydrophilicity of the polymer is decreased. On the other hand, when the temperature increases until higher values than the T_{CP}, the pendant peptide group adopts an extended structure. In this conformation, only the strong intrapendant hydrogen bond (**V1** C=O□□□HN **V4**) is present. This extended structure adopted by the pendant group can be considered as a flatter and less bulky pendant (**Figure 3f**) in which no interpendant hydrogen bonds are feasible. Thus, a more compressed helical scaffold with a significantly smaller helical pitch is adopted (**Figure 3g, h**). This compressed scaffold is in agreement with the hypsochromic shift observed at the UV spectra when the temperature increases. In addition, we could observe how the terminal carboxylic groups of the pendants in this helical structure were exposed towards the solvent, responsible of its hydrophilic behavior in these conditions (**Figure 3e**). As consequence, the macromolecular structure adopted by the PPA can be used as the driving force to explain the non-typical thermoresponsive transition shown for the EBPPA and its atypical pH and concentration dependencies.

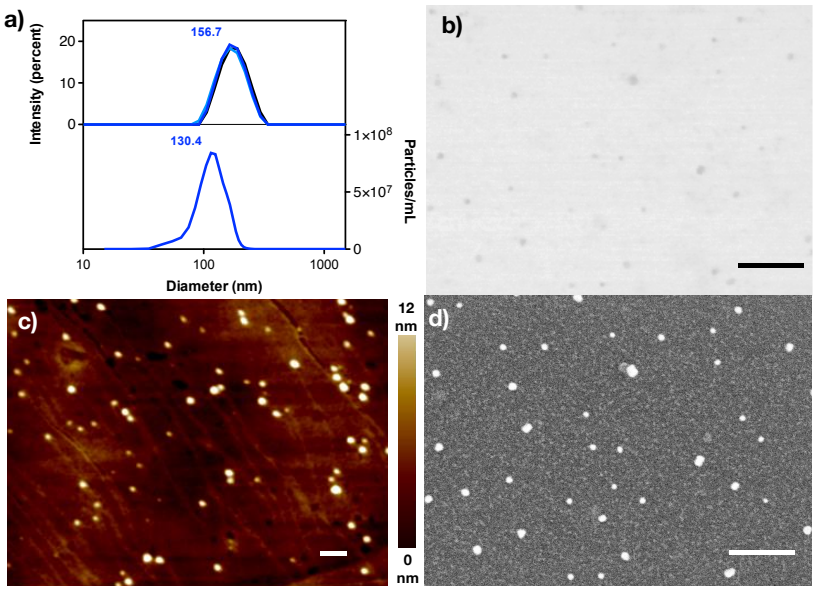

Figure 4. a) Size distribution of poly-**2** by DLS (above) and NTA (below) in water at 25ºC. b) TEM , d) SEM, and c) AFM images. Scale-bars denote 200 nm on TEM and SEM images and 500 nm on AFM.

Various characterization techniques showed that poly-**2** self-assembled in its hydrophobic state into chiral nanoparticles with spherical morphology. For instance, dynamic light scattering (DLS) measurements at 25 ºC and 1 mg/mL showed a mean hydrodynamic diameter of 156.7 nm with a PDI of 0.155. We could observe by nanoparticle tracking analysis (NTA) that the assembled polymer particles had an almost negligible smaller mean value of 130.4 nm at the same temperature but at a concentration of 20 ∓g/mL (**Figure 4a**). The particle morphology was studied under atomic force microscopy (AFM) revealed a spherical morphology with a mean size diameter of 130.7 nm and a mean height of 7.66 nm. The particle morphology was corroborated by scanning and transmission electron microscopy (SEM, TEM), which showed under the high vacuum conditions spherical nanoparticles with a mean diameter of 38.75 nm and a low degree of polydispersity of 0.108 (**Figure 4b, c, d**).

In conclusion, we have prepared a new class of elastin-based side-chain polymers with chiro-thermoresponsive properties. The unexpected USCT thermodynamic behavior of the deprotected water-soluble polymer contrasted to the expected LCST from the natural elastin as well as the previously reported elastin-based side-chain polymers. The observed CD inversion matched with the UV cloud point in temperature dependent CD and UV studies. All these

results suggest that the helical structure adopted by the PPA plays an important role in the thermoresponsive behavior of the pendant chain. The EBPPA are, to the best of our knowledge, the first system where the structure adopted by the polymer skeleton governs the thermopathy of a thermoresponsive protein-based substituent. We rationalized the system thermoresponsivity by modeling a possible macromolecular structure of the EBPPA that helped to a better understanding of the thermal transition process. The inter- and intra-pendant hydrogen bonds on the two simulated helical conformation above and below the transition temperature are considered the driving force of the process. Moreover, the chiroptical thermoresponsive behavior of this EBPPA is accompanied by the formation of spherical nanometric particles in solution at its hydrophobic state.

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AUTHOR CONTRIBUTIONS

S.A. and J.B. performed the synthesis and characterization of the compounds. F.F., S. A., and J. B. generated the molecular model. J.B. conceived the work and wrote the paper. All authors discussed the results, read and commented on the manuscript.

ADDITIONAL INFORMATION

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and

requests for materials should be addressed to J. B.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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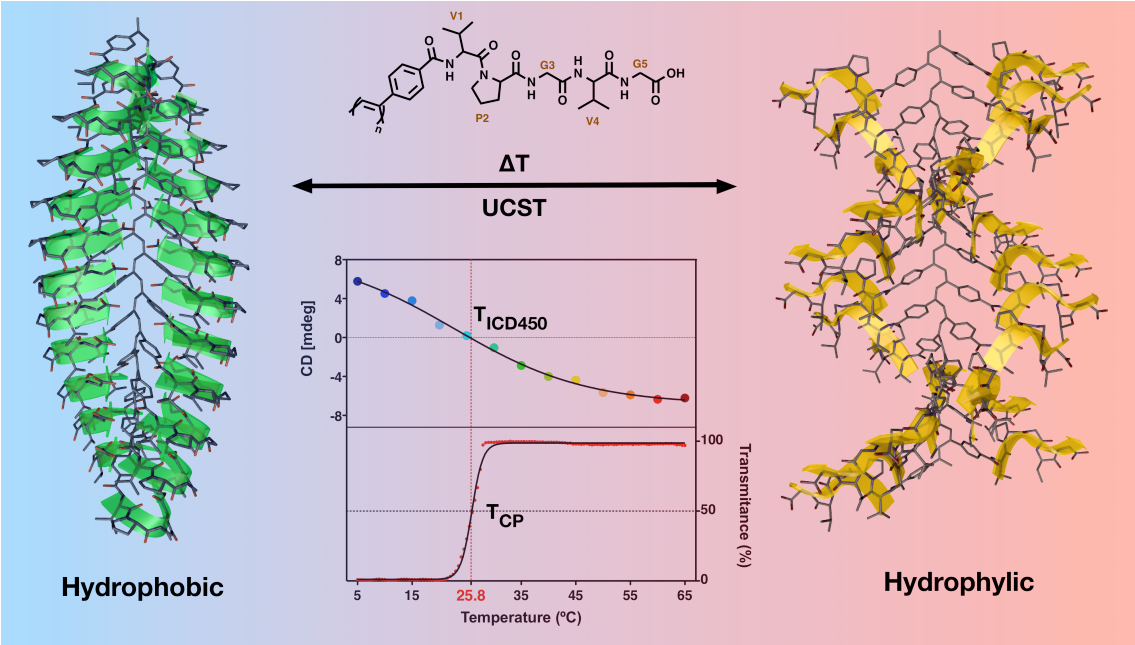

The dynamic macromolecular helical structure of a poly(phenylacetylene) can be used to alter the thermoresponsive properties of an elastin-based side-chain polymer. The polymeric helical conformation changes the expected lower critical solution temperature thermoresponsiveness to an upper critical solution temperature behavior. All the conformational changes can be tracked by changes on the circular dichroism that matches with the transition temperatures.