

# Diastereomeric multi-chiral pendant groups: Their key role in stimuli-responsive polymeric responses

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## Abstract

Chiral information transmission in helical polymers bearing multi-chiral pendant groups is usually determined by the absolute configuration of the first chiral center. The second chiral residue usually has low-to-null influence in the macromolecular handedness of the polymer, due to its remote position respect to the polyene main chain. Here, we demonstrate how the stimuli responsive properties of diastereomeric polymers, obtained by changing the absolute configuration of the second chiral center, are different due to the unlike properties of diastereoisomers.

## KEYWORDS

chiroptical switches, diastereomers, helical polymers, helical stretching, solvent polarity

## 1 | INTRODUCTION

Helical macromolecules have attracted the attention of the scientific community due to the properties and functionalities associated with this structural motif.<sup>1,2</sup> In consequence, a large variety of non-natural foldamers and

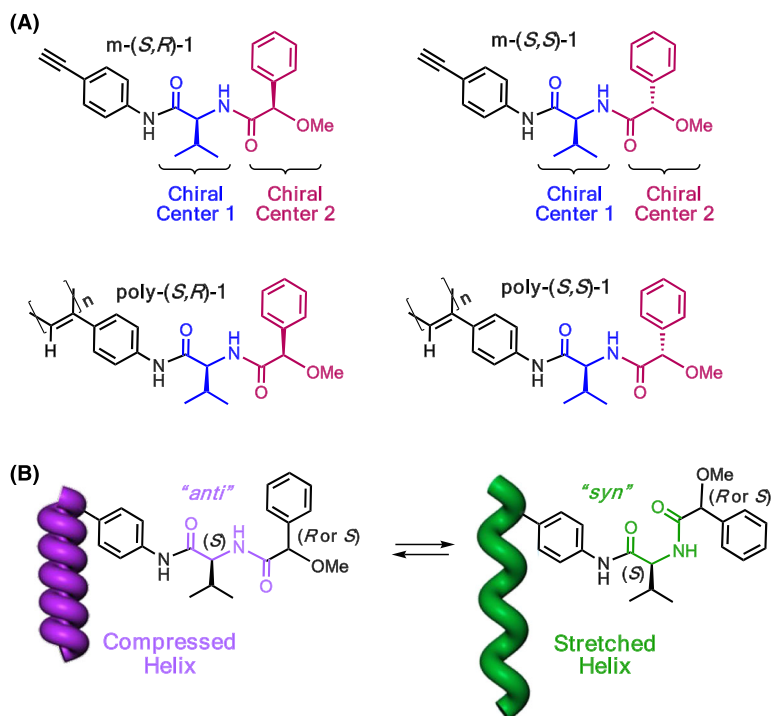
helical polymers have been studied during the last decades. In the special case of helical polymers, families such as poly(isocyanide)s,<sup>3</sup> poly(isocyanate)s,<sup>4</sup> poly(diphenylacetylene)s,<sup>5,6</sup> or polyacetylenes,<sup>7,8</sup> among others, provide a large variety of helical scaffolds with different static/dynamic, which properties find applications in different fields such as chiral materials asymmetric catalysis,<sup>9–13</sup> chiral recognition,<sup>14,15</sup> circular polarized luminescence (CPL) sources,<sup>5,6,15,16</sup> chiroptical switches,<sup>17,18</sup> or chiral stationary phases for high performance liquid chromatography (HPLC) among

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FIGURE 1 (A) Chemical structures of *m*-(*S,R*)-**1**, *m*-(*S,S*)-**1**, poly-(*S,R*)-**1** and poly-(*S,S*)-**1**. (B) *Syn/anti* conformation of the valine residue in poly-(*S,R*)-**1** and poly-(*S,S*)-**1**



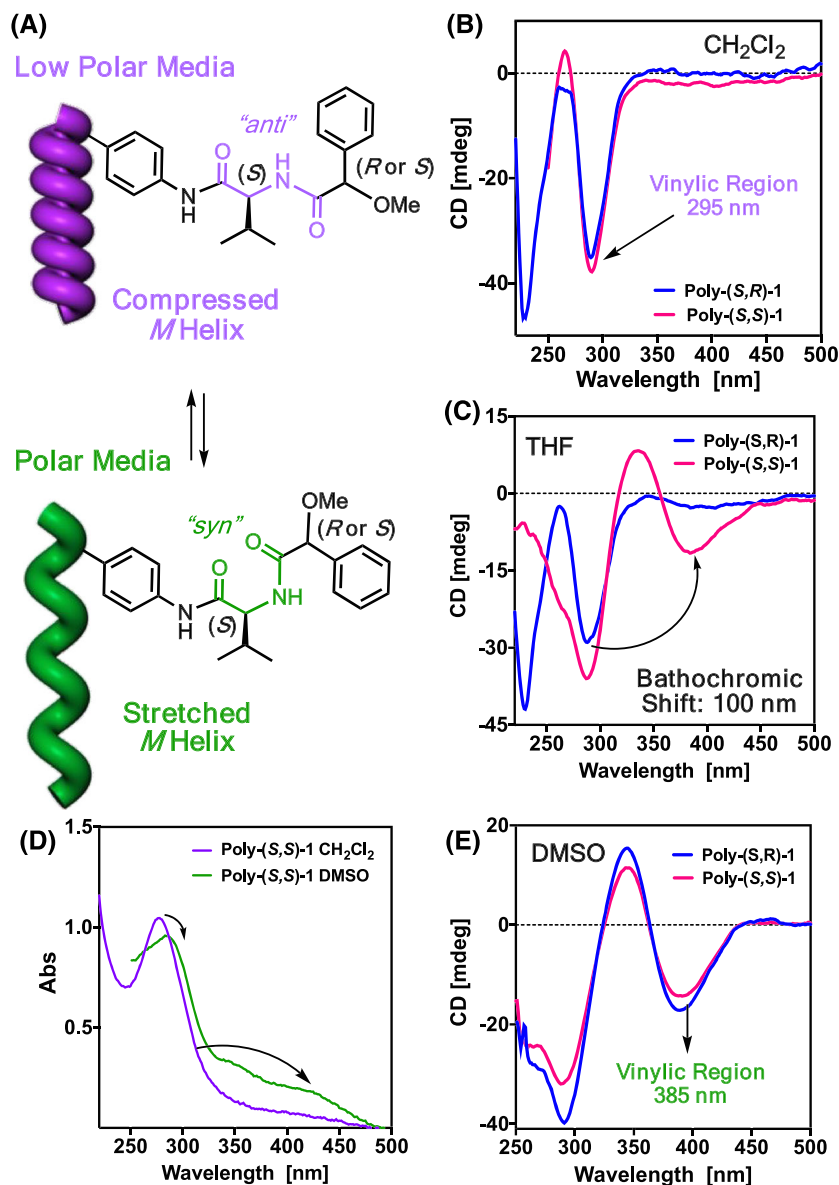
others.<sup>19–21</sup> To be functional, these helical polymers must adopt macromolecular helical structures with screw sense excess. This can be achieved using supramolecular interactions with different external stimuli,<sup>22,23</sup> by controlling the conformational composition of the pendant groups<sup>24–27</sup> or by means of different chiral communication mechanism like Sergeants and Soldiers Effect,<sup>28–31</sup> Majority Rules,<sup>32,33</sup> Chiral Coalition,<sup>34</sup> Chiral Harvesting,<sup>35–37</sup> or Chiral Teleinduction<sup>38</sup> among others.

Most of the screw sense control studies in helical polymers have been done with pendant groups possessing a single chiral center, without paying attention to multi-chiral pendant groups. This fact is due to the control exercised by the first chiral center attached to the polymerizable functional group in the monomer, which is usually located close to the helix backbone in the macromolecular scaffold. This fact makes the other chiral centers present in the pendant group have a low-to-null impact on the net helicity of the system due to their remote location with respect to the polymer main chain.<sup>39–43</sup> Our group has recently developed different protocols to modulate this effect and surpass the command of the first chiral center through a conformational control of the linkage between the different chiral residues. Allowing, in certain conformations, to place the second chiral center close to the polyene backbone results in the so-called chiral overpass effect (Figure 1).<sup>44,45</sup> In particular, we used as pendants dipeptide sequences or peptidomimetics that are involved in structural motifs such as turns, different from the classical  $\beta$ -sheet orientation found in these polymers. As a result, when the pendant adopts a bent conformation, the second

chiral center occupies a position closer to the polymer main chain allowing it to dominate the handedness of the helix.

Herein, we want to explore how the point chirality of the second residue affects the stimuli responsive properties of a poly(phenylacetylene) (PPA) where the first chiral residue commands the helix through the adoption of a  $\beta$ -sheet<sup>46,47</sup> conformation in the pendant group.<sup>38,40,41,43</sup> It is well known that physical and chemical properties of diastereoisomers are different, and therefore, the stimuli responsive properties of diastereomeric PPAs towards solvent polarity can also be different. To study that, we designed a phenylacetylene monomer that bears the anilide of (*S*)-valine connected to the (*R*) or (*S*)- $\alpha$ -methoxy- $\alpha$ -phenylacetic acid (MPA)—*m*-(*S,R*)-**1**, *m*-(*S,S*)-**1**—(Figure 1A). In the corresponding polymers—poly-(*S,R*)-**1**, poly-(*S,S*)-**1**—valine must govern the helix resorting to its two major conformations—*syn* and *anti*—controlled by solvent polarity. The role of the second chiral center is just to alter the polarity of the polymers due to their diastereomeric relationship. As a result, the *syn/anti* conformational control of the valine residue in the two diastereomeric polymers can be produced at different solvent polarities, allowing us to detect a certain solvent.

To test our hypothesis monomers, *m*-(*S,R*)-**1** and *m*-(*S,S*)-**1** were prepared according to the protocol shown in the Supporting Information. Next, the corresponding polymers, poly-(*S,R*)-**1** and poly-(*S,S*)-**1**, were prepared by using a Rh(I) catalyst—(i.e., [Rh(nbd)Cl]<sub>2</sub>)—which produces the desired PPAs with a high *cis*-content of the conjugated double bonds as inferred by <sup>1</sup>H nuclear



**FIGURE 2** (A) Schematic illustration of the helical transformations of poly poly-(*S,R*)-1 and poly-(*S,S*)-1 triggered by polarity effects. Electronic circular dichroism (ECD) spectra in (B) CH<sub>2</sub>Cl<sub>2</sub>, (C) THF, and (D) DMSO. (D) Ultraviolet-visible (UV-vis) spectra of poly-(*S,S*)-1 demonstrating the helical stretching

magnetic resonance (NMR) and Raman (see Figures S7–S9).<sup>48,49</sup>

Electronic circular dichroism (ECD) studies of poly-(*S,R*)-1 and poly-(*S,S*)-1 were carried out in solvents with different polarity such as CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, THF, DMF, and DMSO (Figure 2). In low polar solvents, for example, CH<sub>2</sub>Cl<sub>2</sub> and CHCl<sub>3</sub>, both polymers show ECD traces composed of two strong negative Cotton effects with maxima at 228 and 288 nm that corresponds to a compressed *M* helix.<sup>50,51</sup> This structure is adopted when the two amides of the valine residue are *anti* oriented, conformation that is favored for PPAs derivatized with amino acids in low-polar solvents (Figure 2A).<sup>52,53</sup> To corroborate the presence of a helical structure, optical rotation (OR) measurements were done for poly-(*S,R*)-1 and poly-(*S,S*)-1 in CH<sub>2</sub>Cl<sub>2</sub> and the corresponding monomers. The values obtained for the polymers are much

higher than those obtained for the monomers, indicating the presence of a helix (see Table S3).

Interestingly, the ECD traces obtained for poly-(*S,R*)-1 and poly-(*S,S*)-1 in a medium polar solvent like THF are completely different. Thus, whereas poly-(*S,R*)-1 shows a spectrum similar to that obtained in low polar solvents (see above), poly-(*S,S*)-1 shows a more stretched helix with three consecutive and alternating  $-/+/-$  Cotton effects with maxima at 280, 345, and 390 nm (Figure 2C), indicating the adoption of a preferred stretched *M*-helix.<sup>50,51</sup> This helical stretching is associated to an *anti* to *syn* conformational change at the valine residue, conformation favored in PPAs derivatized with amino acids in polar solvents.

Therefore, both polymers show different stimuli responsive properties towards THF due to their diastereomeric relationship.

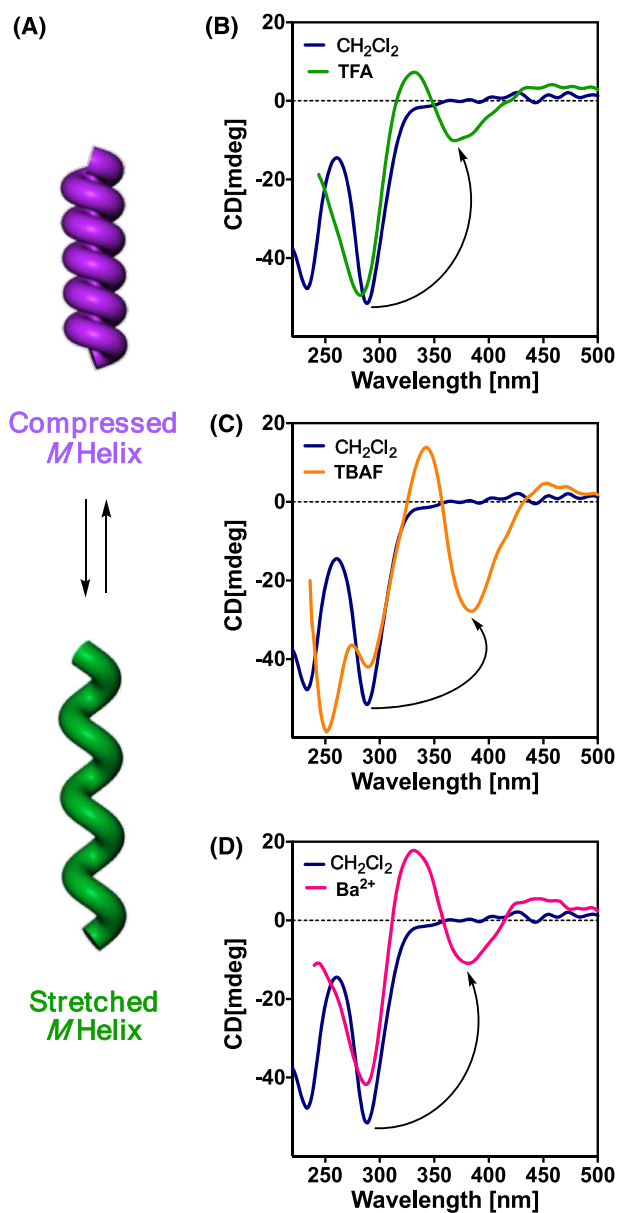


FIGURE 3 (A) Schematic illustration of the elongation of poly-(*S,S*)-**1** monitored by electronic circular dichroism (ECD) after interacting with (B) TFA, (C) TBAF, and (D) metal coordination (i.e.,  $\text{Ba}^{2+}$ ) (0.3 mg/mL,  $\text{CH}_2\text{Cl}_2$ )

When analogous ECD studies are carried out in more polar solvents such as DMSO or DMF, both polymers show similar ECD traces with three consecutive and alternating  $-/+/-$  Cotton effects with maxima at 280, 345, and 390 nm, virtually identical to that observed for poly-(*S,S*)-**1** in THF. As a result, poly-(*S,R*)-**1** and poly-(*S,S*)-**1** adopt stretched *M*-helical scaffold in polar solvents due to the *syn* conformation of the valine residue.

Comparison of the ultraviolet–visible (UV–vis) spectra for poly-(*S,R*)-**1** and poly-(*S,S*)-**1** in  $\text{CH}_2\text{Cl}_2$  and DMSO shows a large bathochromic shift of the polyene band from 310 nm in  $\text{CH}_2\text{Cl}_2$  to 425 nm in DMSO in

agreement with the ECD observations (Figures 2D and S12).

Next, we decided to demonstrate the presence of the *anti* to *syn* conformational change by adding different stimuli such as TBAF, TFA, or  $\text{Ba}(\text{ClO}_4)_2$  to a  $\text{CH}_2\text{Cl}_2$  solution of poly-(*S,R*)-**1** and poly-(*S,S*)-**1**. From previous studies, it is known that these stimuli produce conformational changes at the pendant, *anti* to *syn*, by interacting with the amide groups.<sup>44,52,53</sup> Here, we showed that the compressed *M*-helix is transformed into the stretched one when these stimuli are present,<sup>54,55</sup> corroborating the *anti* to *syn* conformational change at the pendant (Figure 3A–C).

## 2 | CONCLUSION

In conclusion, we have demonstrated that although the helical senses induced in helical polymers possessing multichiral pendant groups is governed by the chiral center placed closer to the backbone, the other chiral centers placed in remote positions can have important consequences in the stimuli responsive properties although their influence in the helical sense induction is limited. In this work, two different PPAs bearing as pendant (*S*)-valine-(*R*)-MPA and (*S*)-valine-(*R*)-MPA were prepared. The helical sense in all the solvents tested is commanded by the (*S*)-valine, obtaining a *M* helix in all cases. However, this helix is compressed in low polar solvents and stretched in polar solvents, difference attributed to an *anti* to *syn* conformational change produced at the pendant group. This *anti* to *syn* conformational change is activated by the solvent polarity, and because the two diastereomeric polymers, poly-(*S,R*)-**1** and poly-(*S,S*)-**1**, have different physical properties, the value of the dielectric constant of the solvent needed to produce this conformational change is different for both polymers. As a result, these two polymers show different stimuli responsive properties in THF. Whereas poly-(*S,R*)-**1** adopts a compressed helix due to an *anti*-conformation at the pendant, in poly-(*S,S*)-**1**, an *anti* to *syn* conformational change is triggered producing a stretched helix. Consequently, these two polymers allow to sense THF due to the different helical scaffolds induced by a different conformational composition at the pendants. We believe these findings will encourage the scientific community to study more complex multi-chiral pendant groups and their potential impact in the folding/stimuli-responsive nature of the polymers. Efforts in that direction are currently ongoing in our laboratory.

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## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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