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Hydrophobically driven twist sense bias of hollow helical foldamers of aromatic hydrazide polymers in water

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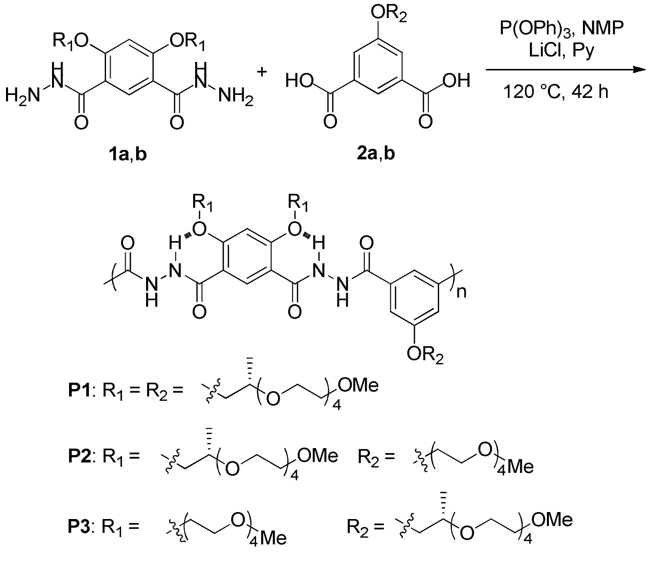
Abstract. Three aryl hydrazide foldamer polymers, which bear different number of chiral pentaethylene glycol chains, have been synthesized. Circular dichroism and UV-vis studies reveal that two of them can be driven by the hydrophobicity to form helical hollow conformation in water that exhibits a strong twist sense bias.

In the past two decades, there has been considerable interest in the development of hollow foldamers, linear molecules that fold into helical conformations of well-defined cavity.[1-4] Such hollow molecular helices can exhibit helicity bias induced by chiral subunit(s) attached to the ends or middle of the backbones,[5] or side chains,[6] or by chiral guests through selective binding.[7] Extending the backbones would produce long chiral single molecular tubes that may exhibit new functions in, such as, stereoselective recognition and encapsulation, ion transport and catalysis.[2f,8] In this context, polymeric backbones may be prepared by one-step condensation of rationally designed monomers bearing chiral subunits. Such a strategy not only avoids the time-consuming multi-step synthesis for molecular foldamers of the fixed length, but also makes it possible to prepare very long backbones for the formation of macromolecular tubes with extended depth. By using intramolecular hydrogen bonding as the driving force, Meijer and co-workers had constructed chiral poly(ureidophthalimide) foldamers,[9] and Zhu and co-workers had generated chiral arylamide polymeric foldamers.[10] Herein, we describe that hydrophobicity can be used as the driving force to induce aromatic hydrazide polymers to fold into tubular helices in water with strong twist sense bias.

Previous study revealed that, in the absence of successive intramolecular N–H···X (X = O, N, F) hydrogen bonding,[2f] aromatic amide oligomers did not fold into helical conformations.[11] We thus prepared polymers **P1-3** from the condensation reactions of the corresponding precursors **1a**,**b** and **2a**,**b** under the Yamazaki polymerization conditions (Scheme 1).[12] Every 4,6-alkoxylisophthalamide segment forms two strong intramolecular six-membered N–H···OR hydrogen bonds,[2f] which partially rigidified the backbones of the polymers and was expected to facilitate the designed hydrophobicity-induced folding.[10] All the three polymers were soluble in water as well as common organic solvents, including dichloromethane, chloroform, methanol and ethanol. The number-average molecular weights (M_n) of polymers **P1-3** were determined by the gel permeation chromatography (GPC) to be 14365, 12209 and 7201, respectively, whereas their weight-average molecular weights (M_w) were determined to be 31200, 31087 and 21495, respectively. These values correspond to the molecular-weight dispersity of 2.17, 2.55 and 2.99, which suggest these polymers consisted of chains with a modest distribution of lengths. These results indicate that the polyamide chains had an average length of 26, 24, and 14 aromatic subunits, respectively. These values suggest that polymers **P1** and **P2** have about four helical turns, assuming that one turn consists of six aromatic subunits, whereas polymer **P3** has about two helical turns, if the helical conformation is formed (vide infra, Fig. 4). For comparison, we also prepared 3-mer **O1** and 7-mer **O2**, which have three and seven aromatic subunits. Longer folded **O2** was expected to form a helix of more than one turn.



Scheme 1 Synthesis of polymers **P1**, **P2**, and **P3**.

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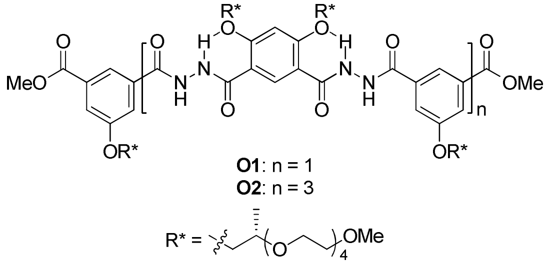

O1: n = 1
O2: n = 3

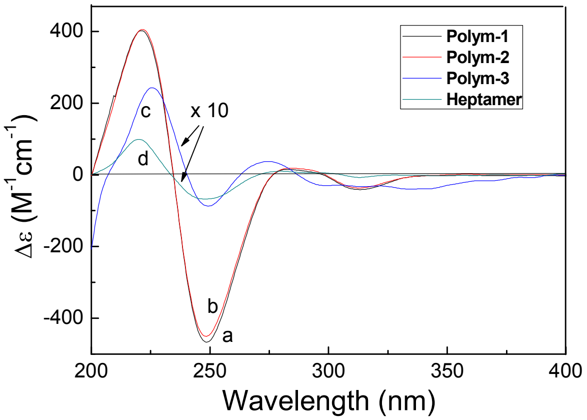

Fig. 1 CD spectra of polymers a) **P1**, b) **P2**, c) **P3** and d) 7-mer oligomer **O2** in water at 25 °C. The concentration of the repeat aromatic subunits (two benzene rings) was 50 μM.

Both polymers and oligomers were soluble in polar solvents. Their circular dichroism (CD) spectra in polar organic solvents and water were recorded. In all organic solvents used, including methanol, ethanol, dioxane, and acetonitrile, neither of them exhibited discernible CD signals, suggesting no helicity bias if helical conformations were formed. In water, the three polymers and 7-mer oligomer **O2** all exhibited one bisignate Cotton effect. The spectra are provided in Fig. 1. For comparison, the concentration of the repeat aromatic subunits (two benzene rings) of the polymers and oligomer was all kept at 50 μM. These observations support that all the polymers and oligomer formed helical conformations with helicity bias in water. The positive and negative maxima of this bisignate effect of **P1** and **P2** were nearly identical, and the zero-crossing at 234 nm coincided with the absorption maximum of the aromatic rings in the UV-Vis spectrum (ESI). For **P1** and **P2**, a small negative CD effect was also observed around 313 nm, which is presumably to be attributed to the 4,6-dialkoxyisophthalamide moiety. The fact that **P1** and **P2** generated nearly identical CD spectra suggests that the chiral side chains on the 4,6-dialkoxyisophthalamide moiety could alone induce the backbones to produce helicity bias and the chiral side chain on the 5-alkoxyisophthalamide moiety had a much lower contribution towards inducing the helicity bias. Changing the temperature from 5 °C to 65 °C caused no important weakening of the CD signals in the spectra of both polymers (ESI), implying that a stable compact helical conformation was already formed at room temperature. Polymer **P3**, which bears chiral chains only on the 5-alkoxyisophthalamide moiety, gave rise to remarkably weak CD signals (Fig. 1), reflecting that the chiral chain on the 5-alkoxyisophthalamide moiety was less efficient in inducing the helicity bias. 7-mer **O2** also generated a very weak bisignate Cotton effect (Fig. 1). The positions of the signals were very close to those of **P1** and **P2**, reflecting that they had the identical helicity bias pattern, but the helical conformation of short **O2** was much less stable due to the fact that only the two aromatic rings at the ends could stack intramolecularly through the helical conformation. As expected, **O1** was CD-silent in water.

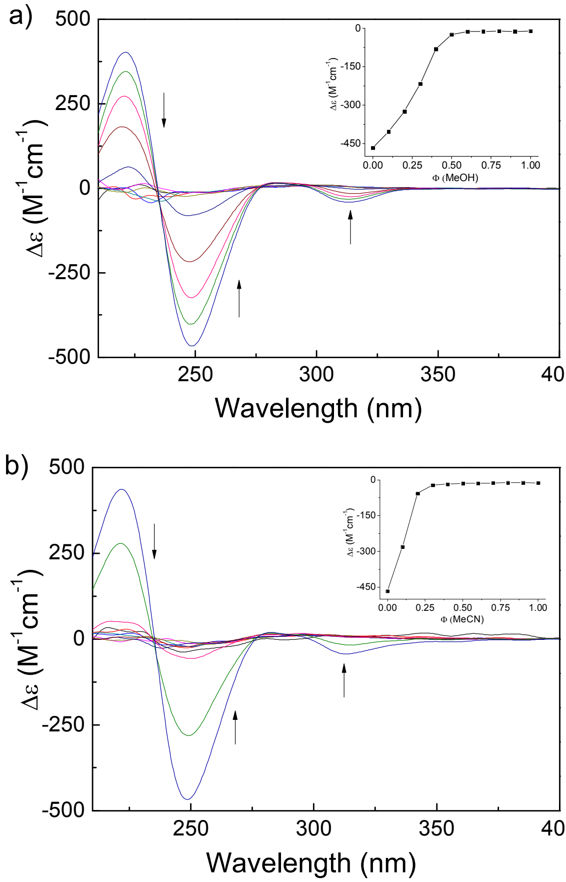

Fig. 2 CD spectra of **P1** in binary (a) methanol/water and (b) acetonitrile/water mixtures at 25°C. The inset: the negative maximum Cotton effect versus Φ. The concentration of the repeat aromatic subunits was 50 μM.

To get insight into the mechanism for the generation of the helicity bias of the polymers, the CD spectra of **P1** in mixtures of methanol and water were recorded (Fig. 2a). With the increase of the content of methanol, the CD signals became weakened gradually and disappeared when Φ (Φ: the relative ratio of the organic solvent) reached 0.5. The weakening clearly reflects the loosening of the intramolecular packing, which gradually permitted helicity inversion and eventually led to the disappearing of the CD signals with the increase of the content of methanol. Similar weakening and disappearing of the CD signals were also observed in mixtures of acetonitrile and water (Fig. 2b). Actually, with a lower content of acetonitrile (Φ = 0.2) added, the CD signals already nearly disappeared. Polymer **P2** also displayed similar CD signal weakening when adding methanol or acetonitrile to its solution in water (ESI), and at Φ = ca. 0.5 and 0.25, the CD signals vanished completely. All these observations support that intramolecular cross-layer hydrogen bonding, which should be enhanced with the increase of the organic solvent in the binary media, contributed little to the stabilization of the helical conformation and thus the

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induction of the helicity bias. We thus propose that the formation of the helical conformation and the helicity bias was mainly driven by the hydrophobic effect which induced the intramolecular stacking of the aromatic backbone of low polarity to minimize the surface area exposed to the polar media. When methanol or acetonitrile was added, the hydrophobic effect became weakened, which led to the loosening of the helical state and the weakening of the helicity bias.

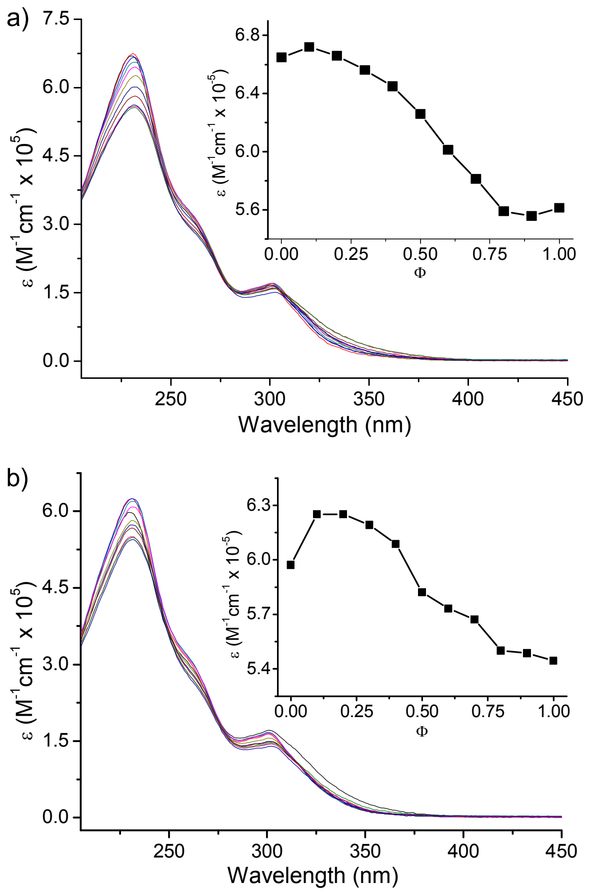
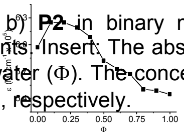


Fig. 3 UV-vis spectra of a) **P1** and b) **P2** in binary mixtures of methanol and water of increasing contents. Insert: The absorbance at 232 nm versus the relative content of water (Φ). The concentration of the repeat aromatic subunits was 25 μM, respectively.



The hypochromic effect is an efficient indicator of the intramolecular stacking of chromophores for aromatic folded systems at highly dilute concentrations which avoid intermolecular stacking.[13] We thus also recorded the UV-vis spectra of polymers **P1-3** in binary mixtures of methanol and water, keeping the concentration constant (Fig. 3 and ESI). For all the three polymers, the absorption became increased after a small amount of water was added. The spectrum then displayed continuous hypochromism with the increase of the water content (Fig. 3, Inset). UV-vis dilution experiments indicate that at the investigated low concentration, no intermolecular stacking occurred. Thus, the above result supports that intramolecular aromatic stacking took place in mixtures with high water content through folding the backbones. The hypochromic effect exhibited by polymer **P3** showed that this polymer also folded into helical conformation in water, even though the chiral side chain on the 5-alkoxyisophthalamide subunit could only induce much weaker helicity bias. The UV-vis spectra of **P1-3** were also recorded in mixtures of acetonitrile and water. Similar hypochromic effect was observed at high content of water, supporting the formation of the helical conformation. In both mixtures, 7-mer **O2** also displayed a weak hypochromic effect, again indicating the formation of a helical foldamer.

To gain information about the preferred helicity of the polymers, MM calculations were performed in vacuo, using the Compass force field, for **P1** and **P2**. The models contained four turns with twenty-four aromatic subunits. For simplification, the two side chains were replaced with shorter (*S*)-(2-methoxy)propoxyl and 2-methoxyethoxyl groups, respectively. All the helical conformers obtained featured intramolecular aromatic stacking in the range of 3.3-3.8 Å and two intramolecular six-membered hydrogen bonds for the 4,6-dialkoxyisophthalamide subunits. The results showed that, for both polymers, the M conformer was energetically preferred over the P conformer (Fig. 4 and ESI), and the total potential energy differences were −18.8 and −9.7 kcal/mole, respectively. Notably, the whole aromatic backbone produces a triangular tube with size of about 1.3 nm.

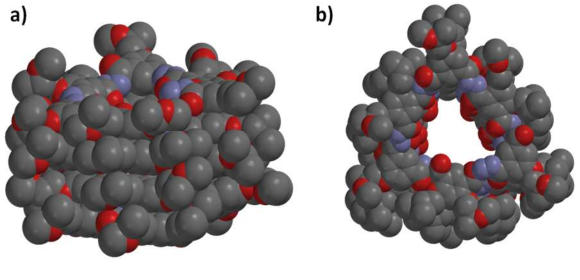


Fig. 4 Optimized preferential M helical conformer of **P1** by the molecular mechanics calculation: a) side-view and b) top-view (C, grey; N, blue; O, red). The hydrogen atoms were omitted for clarity.

In summary, we have demonstrated that the hydrophobicity can drive partially rigidified aromatic hydrazide polymers to form helical hollow structures with strong helicity bias in water. Notably, the production of this helicity bias is not assisted by cross-layer intramolecular hydrogen bonding. Because the hydrophobicity is the only driving force in water, other kinds of aromatic amide backbones may also be used to construct new chiral polymeric tubes with varying cavity and depth. Further modification of the side chains may lead to the formation of functional tubular systems for stereoselective molecular recognition and encapsulation and transport.

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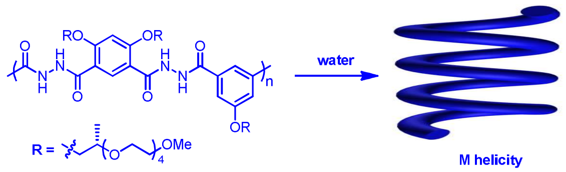

Aromatic hydrazide polymers bearing S-chiral tetraethylene glycol chains can fold into M hollow helices in water driven by the hydrophobicity

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