A Mechanistic Review and Comparison of Achiral Helical Polymers to Conventional Chiral Stationary Phases for Enantioselective Separation

TBIOMD 492

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INTRODUCTION

- Many biologically active molecules, especially drugs, are chiral, meaning they are non-superimposable mirror images. More than half of all drugs are chiral compounds, and 90% are synthesized as racemic mixtures of different images (Inaki et al., 2016; Senkuttuvan et al., 2024).

- Separating these molecules are important, as one enantiomer may be therapeutic, while it's mirror may be inactive or harmful. The greatest example of these differing affects was in the thalidomide tragedy in 1960 (Rajkumar, 2004).

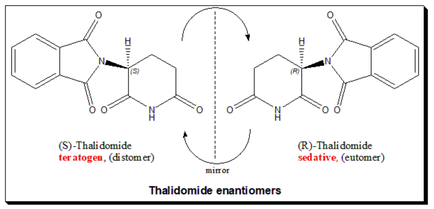

Figure 1: Two enantiomers of Thalidomide. Synthesized as a racemic mix, meaning both exist if not separated. (Senkuttuvan et al., 2024, Inaki et al., 2016). ,

- Traditionally, using (Ultra) High Liquid Chromatography, we can selectively separate mixtures to reach high enantiomeric purity of mixtures, separating on the basis of the mixtures affinity with Chiral Stationary Phases (CSPs). (Sahu et al. 2018)

- Consistent research on alternative CSPs is rampant, as most CSPs are expensive, have limited accessibility and fluidity, with limited selectivity, only interacting with molecules with stereospecific interactions. No single CSP can resolve all analyte classes, which can end up becoming extremely costly in the long term for all laboratories of varying budgets. (Ikai et al., 2006; Fernandes et al., 2021, Papp et al., 2024 .)

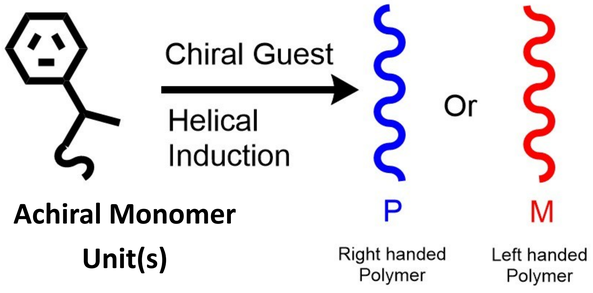

Figure 2: Diagram representing differing handed polymers by notation of P and M. Achiral monomer is used to synthesize a long string of polymers, then made helical (Salazar, 2025).

- Achiral Helical Polymers are potentially cheaper alternatives to traditional CSPs, utilizing unique and adaptable mechanisms to achieve differing results. (Yashima et al., 2017; Zhang & Deng, 2020, Ikai et al., 2006)

- Being synthesized with cheaper achiral monomeric units and interacting with a chiral guest, they can exhibit chiral properties similar to, if not better than popular current CSPs. (Yashima et al., 2017; Ikai et al., 2006)

OBJECTIVE

In this literature review, I sought to analyze previous and current research on achiral helical polymers and whether or not they could compete against currently utilized CSPs for enantioselective recognition. I also explored other alternative use cases for achiral helical polymers outside of only research settings.

MECHANISMS

HELICITY AND MEMORY

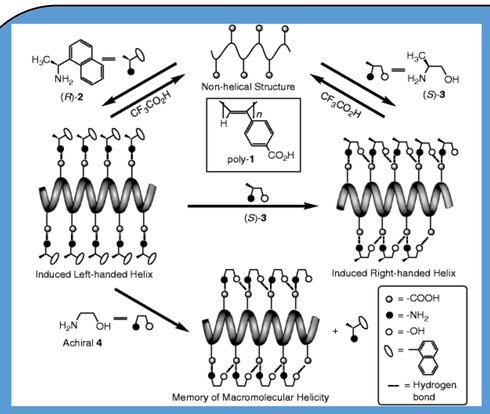

Figure 3: Figure adapted from Yashima et al 1999, showing helical induction of a non-helical achiral polymer, along with the chiral guests of choice as well as alternatives for induction and retaining macromolecular memory.

- **Molecular helicity can be induced through the usage of a chiral guest, taking an otherwise non-helical polymer of achiral monomers and inducing a handed helicity, differing depending on the chiral guest of choice** (Takashi Kaneko et al. 2012, Yashima et al. 1999)
- **Despite the removal of a chiral guest, an achiral helical polymer can continue to exist and function the same with it's memory of macromolecular helicity, maintained by fine tuning the conditions of the environment** (Yashima et al., 2017).
- **While requiring extensive research, perfect long term memory of a handed helicity is plausible, however varying on monomer, chiral guest, and environment** (Madea et al., 2004).
- **It was further discovered that induced helicity can have various complex mechanisms, where in research by Miyagawa et al. (2005), they had synthesized an achiral helical polymer, capable of inverting it's helix handedness through heating and cooling after helical induction, retaining memory despite various subsequent rounds of induction reversal.**
- **These conclusions set up an understanding that helical induction and memory mechanisms can vary in complexity and depth, allowing achiral helical polymers to be malleable on basis of situations** (Yashima et al., 2017).

ENANTIOMERIC SEPARATIONS

- **Once helically induced, these polymers can be utilized as CSPs to separate racemic mixtures enantiomerically** (Ikai et al., 2023).
- **Contrasting traditional CSPs that utilize mainly stereospecific interactions for separations, helical polymers utilize geometrical conformation, allowing molecules, or in this case, differing enantiomers to bind to helical cavities or grooves across the polymer, creating a chiral environment for binding while not being inherently chiral by definition** (Ikai et al., 2023).
- **Similar to traditional CSPs, the helical polymer must be placed in a stationary form to be utilized by an HPLC, the most common method being a coating of the helicies on silica gel to prevent the dissolving and swelling of certain polymers through immobilization** (Okamoto, 2015).
- **Helical polymers are well suited for recognition of amino acids, some configurations achieving <0.005% ee's.** (Ohta & Inoue, 2002).
- **In comparison to traditional CSPs in enantiomeric separation of racemic mixtures, certain helical polymers showed the same to superior purities than commonly used CSPs, indicating that helical polymers are just as capable than traditional CSPs in the right contexts** (Ikai et al., 2021).

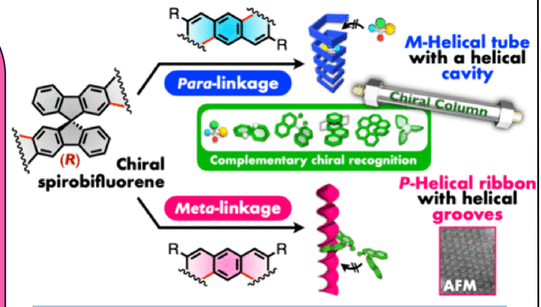

Figure 4: Adapted from Ikai et al, 2025, a visualization of an achiral polymer being induced with helicity and it's two meta and para linkages depending. The M-helical polymer is shaped as a tube, utilizing it's helical cavity for geometric interactions, while the P-helical polymer utilizes its helical grooves for binding, each binding different respective molecules depending.

PENDANT GROUPS

- **Helical polymers can utilize additional pendant groups to manipulate the polymer. The addition of varying molecular structures to the main polymer backbone can significantly change the configuration of the helical polymers' molecular interactions and thermal properties** (Boyle et al., 2019).
- **Pendants can induce a significantly more pronounced effect in enantioselective recognition, being capable of changing conformational changes, chiral biases, and a potential inversion of a helix's handedness** (Frire et al., 2013).
- **Polymers can also utilize chiral pendants to induce helicity inherently without a chiral guest, but offer far less flexibility in tuning recognition** (Ikai et al., 2022).
- **Pendant groups can heavily influence the structure and function of all helical polymers, indicating that polymers can be heavily adjusted depending on the needs or desirable outcomes for a resolution.**

APPLICATIONS

- **Separation of amino acids of drug intermediates, resolving racemic pharmaceutical molecules, and serving as selective binding scaffolding, all uses in medicinal chemistry and biosensing (Ikai & Okamoto, 2000; Yashima et al., 2016).**
- **Potential usage in polymer-based optical sensors (CD or UV-Vis spectroscopy), serving as analytic probes for *in situ* studies requiring live observation of a subject in it's natural environment with real-time monitoring (Green et al., 1995; Yashima et al., 2016). Examples: Measuring changes in biological tissue in real time, tracking treatment delivery, biochemical changes, and disease progression (Castro et al., 2021).**

RESULTS

The differences between traditional CSPs and achiral helical polymers is primarily qualitative, focusing on adaptability and tunability rather than absolute resolution metrics.

ADVANTAGES	LIMITATIONS
- Highly tunable and versatile through various chiral guests, pendant groups, and supramolecular interactions. (Okamoto, 1980; Papp et al., 2024) - Effective in resolving amino acids, small molecules, and variety of racemic mixtures (Okamoto, 2015; Rosetti et al., 2021; Ikai et al., 2021). - Very accessible and easier to synthesize CSPs in the lab rather than buying expensive chiral monomers, expanding lab budgets. (Kaneko et al., 2012; Green et al., 1995) - Potentially more sustainable and creates a stable environment for the helical polymer due to helical memory (Yashima et al., 2016; Green et al., 1995).	- Despite saving budgets by using achiral monomers, highly selective helical polymers are expensive and difficult to upscale, limiting usage (Ikai & Okamoto, 2000). - Designing and synthesizing polymers with specific pendants, functionalities, and geometry requires advanced synthetic effort (Ikai & Okamoto, 2000; Madea et al., 2000). - No one universal helical polymer (Okamoto, 2000). - Stability can vary, as changes in solvent, temperature, or time can disrupt helical memory (Kaneko et al., 2012; Yashima et al., 2016). - Competition in the current market is filled with various polysaccharide– and protein-based CSPs (amylose and cellulose derivatives), so helical achiral polymers must demonstrate significantly higher benefits to replace the current market (Okamoto & Yashima, 1998; Papp et al., 2024).

CONCLUSIONS

Chirality and enantiomers remain biologically significant today, meaning enatioselective separation and recognition tools in pharmaceuticals remains a necessity. While there is a distinction between achiral helical polymers and traditional CSPs in most qualitative metrics, these polymers serve as a complementary rather than an overall replacement for the current market; not competitors, but another option. Further research has and is focusing on further understanding the mechanisms behind these achiral helical polymers, testing the boundaries and possibilities with various pendant setups or potential chiral guests. The more we understand about these mechanisms, the further we can utilize it's potential. With enough research and investment, the vast majority of limitations will become less burdensome, and achiral helical polymers will become far more accessible and practical in both analytical chemistry and medicinal chemistry.

Acknowledgements

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WORK CITED