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Stereochemical Sequence Dictates Unimolecular Diblock Copolymer Assembly

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Abstract

Deciphering the significance of length, sequence, and stereochemistry in block copolymer self-assembly remains an ongoing challenge. A dearth of methods to access uniform block co-oligomers/polymers with precise stereochemical sequences has precluded such studies. Here, we develop iterative exponential growth (IEG) methods for the synthesis of a small library of unimolecular stereoisomeric diblock 32-mers. X-ray scattering reveals that stereochemistry modulates the phase behavior of these polymers, which we rationalize based on simulations carried out on a theoretical model system. This work demonstrates that stereochemical sequence can play a crucial role in unimolecular polymer self-assembly.

Graphical abstract

Chemistry defines stereoisomers as different compounds, and thus, macromolecules that differ by their configuration at one or more stereogenic centers will have different properties. For example, cellulose and starch are stereoisomeric polymers of glucose that have vastly disparate properties and biological functions.¹ In synthetic polymers, the advent of stereoregular α -olefin polymerizations enabled access to polymers with controlled tacticity.²

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Notes

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Supporting Information

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These systems have found commercial utility in the production of high-value polymers such as polypropylene and polybutylene; isotactic, syndiotactic, and atactic polyolefins have varying crystallinities that dictate their mechanical and thermal properties.³ In addition, mixtures of stereodefined polymers can in some cases form stereocomplexes with unique properties.⁴

Chemists have recently focused on techniques that enable access to polymers of discrete length and/or sequence,⁵ which are being actively investigated in energy storage⁶ and biological⁷ applications. Despite these advances, the role of stereochemistry in uniform macromolecular systems has received relatively little attention. For example, though the composition, sequence, and dispersity of diblock co-oligomers/polymers have been investigated recently,⁸ the role of stereochemistry in uniform block copolymer assembly has not, to our knowledge, been systematically studied. A robust strategy for the synthesis of stereochemically pure block copolymers with absolute structural control is a prerequisite for such an endeavor. Herein, we report iterative exponential growth (IEG) methods⁹ that enable the synthesis of a small library of unimolecular stereoisomeric diblock copoly(triazoles) (DPTs). X-ray scattering experiments indicate that the stereochemistry of these DPTs dictates their bulk morphology. These results are rationalized in terms of a theoretical model system that connects stereochemical sequence to variations in the monomer packing radius. This study confirms that stereochemistry should be considered in the design, synthesis, and applications of precision polymers.

Our syntheses of DPTs via IEG¹⁰ rely upon copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions¹¹ to construct the DPT backbone and thiol-ene addition reactions to install sidechain functionalities. Monomers bearing either an azide or a terminal alkyne are derived from glycidal propargyl ether (GPE) in a divergent fashion (Scheme 1A). Following CuAAC, triazole **2** is poised for subsequent cycles of orthogonal desilylation (Scheme 1B, top) and azidification (Scheme 1B, bottom) before another convergent CuAAC. Repetition of this sequence provides access to 4-mers (**4**, $n = 3$), 8-mers (**8**, $n = 7$), 16-mers (**16**, $n = 15$), etc.

The stereogenic centers propagated throughout this IEG sequence are derived from GPE; the enantiomeric excess (ee) of GPE directly impacts the diastereomeric ratio (dr) of each oligomer or polymer synthesized. Our previous route to GPE from commercially available (R)- or (S)-epichlorohydrin (>99.5% ee)^{9b, 10, 12} (Scheme 1C, Method A) provided **GPE-A** in 82% ee in our hands (Figure S19). In this work, (R)- or (S)-epichlorohydrin was treated with propargyl alcohol under Lewis acidic conditions to afford secondary alcohol **S1** (see Figure S1), which was then exposed to sodium hydroxide, affording **GPE-B** in > 99% ee in 71% – 74% yield on ca. 40 g scale (Scheme 1C, Method B).

Chiral HPLC analysis of the four possible stereoisomeric dimers derived from **GPE-B** (**L,L-2B**, **L,D-2B**, **D,L-2B**, **L,L-2B**) and one dimer derived analogously from **GPE-A** (**L,L-2A**) highlighted the importance of the GPE ee (*Note*: in this report, DPTs are drawn from their azide (N) to alkyne (C) terminus; L and D labels are used to indicate the stereochemistry of each unit – wedge and dash bonds, respectively– akin to polypeptide nomenclature). The chromatogram for the dimer derived from **GPE-A** showed three peaks

(Figure 1A); the dr of the major species **L,L-2A** was 84:16. In contrast, the chromatograms for the four dimers derived from **GPE-B** showed a single peak ($> 99:1$ dr) (Figure 1B, Figure S20). These results verify the stereochemical purity of dimers derived from **GPE-B**, and suggest that the propagation of stereochemical impurity from **GPE-A** matches what is predicted by the Horeau Principle ($dr_{\text{dimer}} = (0.91)^2 = 83:17$).¹³ Following this logic, and assuming that undesired diastereomers are not removed during purification, 5 cycles of IEG starting from **GPE-A** would yield a 32-mer, **32A**, with a theoretical dr for the desired diastereomer of only 4.9:95.1 (Figure S21).^{13–14}

With access to **GPE-B**, we synthesized four stereoisomeric DPTs: **L/L-32B**, **D/L-32B**, **alt/L-32B**, and **alt/alt-32B** (Figure 2). The structures of each of these compounds were confirmed by ¹H and ¹³C NMR spectroscopy (Figures S2 – S18) as well as MALDI-TOF mass spectrometry (Figure S22). The thermal properties of the four DPTs were analyzed by differential scanning calorimetry: no dramatic differences were observed in the T_g (-4.8 °C to $+1.1$ °C) between the samples containing at least one homochiral (isotactic) block (Figure S27A-C). **Alt/alt-32B** displayed a T_g at -4.1 °C as well as T_m at 37 °C and 69 °C (Figure S27D), suggesting crystallinity in this syndiotactic DPT.

The bulk morphologies of **L/L-32B**, **D/L-32B**, **alt/L-32B**, and **alt/alt-32B** were assessed by small-angle x-ray scattering (SAXS) after thermal annealing (90 °C for 2 h, ~ 100 mTorr) samples dropcast from a concentrated CH_2Cl_2 solution ($\sim 250 - 500$ mg/mL). Previously, we observed a hexagonal cylinder (HEX) morphology for **32A** with 12.6 nm domain spacing (q) and higher-order reflections at $\sqrt{3}q$ and $2q$.¹⁰ Broad structure-dependent features were also observed in the high- q region: one corresponding to 3.0 nm was attributed to the average distance between two DPT backbones (α), which reflects the extent of sidechain interdigitation; another corresponding to 0.45 nm was attributed to the average monomer-to-monomer distance, which reflects the backbone conformation (β).

The 1D SAXS intensity plots for **L/L-32B**, **D/L-32B**, and **alt/L-32B** (Figure 3) were indexed to three distinct phases: double- gyroid (GYR, $d = 13.4$ nm), lamellar (LAM, $d = 13.6$ nm), and HEX ($d = 12.8$ nm), respectively (Figure 3A – C; see Figures S28 – S30 for supplemental transmission electron microscopy images). Strikingly, a reflection of one homochiral TEG block from L to D (i.e., **L/L-32B** to **D/L-32B**) was sufficient to switch from GYR to LAM. In addition, the impact of stereochemical purity is demonstrated by consideration of the effectively atactic **32A**, which produces a morphology that is more similar to **alt/L-32B** (HEX, $d = 12.6$ nm and 12.8 nm, respectively) than its target structure: **L/L-32B** (GYR, $d = 13.4$ nm). Analysis of the WAXS regions for these same three samples revealed α values from $3.02 - 3.06$ nm, but constant β values of 0.44 nm, which suggests that the deviations observed in the domain spacings ($12.8 - 13.6$ nm) are due to stereochemistry-driven changes in the extent of sidechain interdigitation/packing.

We noted a difference in the 1D SAXS/WAXS intensity plots for **alt/alt-32B** (Figure 3D) compared to the other **32B** DPTs, which reflects the DSC results discussed above. Rather than a sharp principle peak in the low- q region (Figure 3A – 3C), **alt/alt-32B** displayed a broad principle peak ($d = 16.3$ nm) without any higher order peaks, which is indicative of weak long-range order. In addition, sharp peaks were observed at high q values ($d = 2.28$

nm) that we attribute to crystallization of the decane sidechains. An estimation of $T_{ODT} = 50\text{ }^{\circ}\text{C} - 60\text{ }^{\circ}\text{C}$ for **L/L-32B**, **D/L-32B**, and **alt/L-32B** (Figure S31), which is lower than the T_m for **alt/alt-32B** (as assessed by VT-SAXS and DSC, respectively, Figures S31 and S27D), suggests that the initial onset of crystallization prevents subsequent formation of order via phase-separation. The bulk phase behavior of **alt/alt-32B** resembles recent studies from Zuckermann and coworkers on polypeptoid self-assembly where side-chain crystallization, rather than bulk phase separation, leads to lamellae with small domain spacings.^{5c, 8a} Similarly, Meijer and co-workers recently reported on oligodimethylsiloxane-*b*-oligo(L)lactides that crystallize and assemble into lamellae.^{8d, 15} Here again, our results show how stereochemistry can lead to dramatic changes in DPT assembly, switching from crystalline to amorphous materials.

Small-molecule additives are often used to modulate the phase behavior of diblock copolymers.¹⁶ To investigate how chiral additives might impact the assembly of our chiral DPTs, we doped **32B** samples with super-stoichiometric quantities (16 equiv, ca. 20 wt%) of (L)-tartaric acid in an attempt to selectively swell the hydrophilic (TEG) block and thus access new morphologies through horizontal translation across the diblock copolymer phase diagram (Figure 3E – G). Addition of (L)-tartaric acid induced phase transitions from GYR to LAM (**L/L-32B**) and HEX to GYR (**alt/L-32B**) with a concomitant increase in domain spacing (14.4 nm – 14.8 nm) and α (3.46 – 3.63 nm) (β remains unchanged). These results are consistent with a small modification of volume fraction in a sensitive region of the phase diagram. Interestingly, **D/L-32B** remained lamellar (14.8 nm domain spacing, $\alpha = 3.47$ nm), presumably due to the large fraction of phase space occupied by this morphology. Lastly, blending of (L)- tartaric acid with **alt/alt-32B** suppressed crystallization and induced long-range order to provide a lamellar structure ($d = 13.2$ nm domain spacing, $\alpha = 3.36$ nm).

The observed dependence of DPT phase morphology on stereochemical sequence indicates that stereochemistry plays a role in mediating the inter- and intramolecular interactions within these copolymers. Stereogenic centers and their sidechains occupy volumes with specific shapes that constrain their external interactions. Here, we use molecular dynamics simulations of a bead-and-spring diblock copolymer model to explore the effect of chirality on phase morphology.¹⁷ The simulations include a condensed phase melt of model polymers that each consist of 32 individual monomers organized into two blocks, with 16 A-type monomers and 16 B-type monomers. Along with its chemical identity (i.e., A or B), each monomer is assigned a chirality, either (L) or (D), which results in four distinct monomer types, i.e., (L)-A, (D)-A, (L)-B, and (D)-B. The non-bonded monomer-monomer interactions are described with a pair potential that is characterized by an interaction diameter, σ , and an interaction energy, ϵ . The values of these model parameters depend on the identity of the monomers involved in the interaction. To describe the interaction energy, we use a standard symmetric diblock copolymer model for which $\epsilon_{AA} = \epsilon_{BB} = -1$ (in reduced units) and $\epsilon_{AB} = \epsilon_{BA} = -1 + \gamma$, where γ is a positive constant that specifies how much less favorable AB interactions are compared to AA or BB interactions. We include the effects of chirality in the quantity σ . We assume decane and TEG are of similar size, i.e., $\sigma_{AA} = \sigma_{BB} = \sigma_{AB} = 1$ (in reduced units), but that these values vary slightly depending on the chirality of the monomers. Specifically, when monomers differ in chirality, regardless of

their block identity, the interaction diameter is increased by a factor of 1.1. That is, we assume that monomers of differing chirality pack less efficiently and thus interact through an extended effective diameter.¹⁸

We simulated the phase behavior of diblock copolymer melts with a variety of stereochemical sequences; Fig. 4 contains the results of simulations carried out on seven different A/B diblock copolymer melts: isotactic/syndiotactic (e.g., **alt/L-32B**), isotactic/disyndiotactic, isotactic/atactic, syndiotactic/di-syndiotactic, syndiotactic/syndiotactic (e.g., **alt/alt-32B**), isotactic/isotactic (e.g. **L/L-32B**), and disyndiotactic/disyndiotactic. Here disyndiotactic refers to alternating pairwise (L) and (D) monomers (i.e., ...LLDD...). We differentiate phase morphologies based on the radial distribution function, $g(r)$, computed for monomers of the same block-type. The length scale over which $g(r)$ decays to unity roughly indicates block domain size within the melt.

As Fig. 4 illustrates, the phase behavior of our simulated systems depends on stereochemical sequence. We observe that systems with one isotactic block and one block of mixed stereochemistry tend to form phases with block domains that are more extended than those in systems where both blocks are isotactic or syndiotactic. We observe these differences for the case where monomer interaction energies are block independent ($\gamma = 0$), and also when A-B interactions are directly penalized ($\gamma = 1$).

The results in Fig. 4 suggest that effective variations in interaction radius arising from stereochemical mismatch can affect phase morphology across a range of different diblock copolymer compositions. In systems with relatively low degrees of polymerization that are located in a region of the phase diagram that includes several nearby morphologies, stereochemistry can significantly influence bulk properties. The equilibrium phases of mismatched stereochemistries are significantly different than those of purely isotactic copolymers, but matched stereochemistries do not exhibit the same shift in the order-disorder transition.

Despite the fact that biological polymers are chiral and that tacticity has an overwhelming impact on the physical properties of synthetic polymers, little effort has been made to elucidate the underpinnings of stereochemistry in unimolecular synthetic polymers. This work highlights the utility of unimolecular DPT synthesis via IEG and establishes the fundamental role of diastereomeric interactions in unimolecular diblock copolymer self-assembly, proving that it is possible to modulate bulk self-assembly solely through careful stereochemical manipulations. In turn, these results outline the requisite framework for the rationale design of even more elaborate unimolecular systems for specific advanced applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18. We found that the structure of the diblock copolymer melt was sensitive to both energetic and packing effects, but much more sensitive to the latter. See SI for additional information about the model.

Figure 1. Chiral HPLC traces of **A**: dimer derived from GPE-A, (*L,L*-2A, 84:16 dr) and **B**: dimers derived from GPE-B (*L,L*-2B, *L,D*-2B, *D,L*-2B, *D,D*-2B >99:1 dr).

Figure 2.

Structures of stereoisomeric 32mers accessed by IEG from **GPE-B**. The stereochemistry depicted for each repeating unit refers to the stereochemistry of **GPE** from which that monomer was derived. **GPE** = glycidal propargyl ether, TEG = tri(ethylene)glycol.

Figure 3.

1D intensity SAXS and WAXS plots for stereoisomeric **32Bs** with or without (L)-tartaric acid addition. SAXS = small angle X-ray scattering, WAXS = wide-angle X-ray scattering, GYR = gyroid, LAM = lamellar, HEX = hexagonal cylinder. ■ = scattering from Kapton.

Figure 4.

The radial distribution function, $g(r)$, as a function of length (r) computed for monomers of similar block type, from simulations of model A/B diblock copolymers with different stereochemical sequences. Insets contain simulation snapshots of A/B copolymer melts, with black and red beads representing the positions of A-type and B-type monomers, respectively. These snapshots serve to illustrate qualitative differences in the morphology of the simulated systems. iso = isotactic, syn = syndiotactic, disyn = disyndiotactic

Scheme 1.

A *i*. *n*-BuLi then TIPS-Cl, THF, -78°C – rt, 4 h, 85% – 86%; *ii*. NaN_3 , AcOH, DMF, 70°C , 80% – 82%; *iii*. Allyl-Br, NaH, DMF, 0°C – rt, 16 h, 70% – 80%; *iv*. *t*-BuOH, $\text{Mg}(\text{ClO}_4)_2$, rt, 72 h, 91%; *v*. Allyl-Br, NaH, DMF, 0°C – rt, 16 h, 90% – 92%; *vi*. H_3PO_4 (85%), rt, 4 h, 78% – 80%; *vii*. TsCl, DMAP, Et_3N , CH_2Cl_2 , 0°C – rt, 78% – 84%; *viii*. LiBr, DMF, 45°C , 16 h, 86% – 88%. **B**: *iv*. TBAF, THF, 15 min; *v*. NaN_3 , DMF, 35°C , 16 h; *Typical CuAAC*: $\text{Cu}(\text{MeCN})_4\text{PF}_6$, TBTA, sodium ascorbate, CH_2Cl_2 or CHCl_3 . **C**: *Method A* (**GPE-A**): Propargyl alcohol, TBAHSO₄, pentanes / NaOH (aq); *Method B* (**GPE-B**): Propargyl alcohol, $\text{BF}_3\cdot\text{Et}_2\text{O}$ then NaOH, 0°C – rt, 2 h, 71% – 74%.