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Citation for published version (APA): Jansen, S. A. H., Su, H., Schnitzer, T., Vantomme, G., & Meijer, E. W. (2023). Temperature Directs the Majority-Rules Principle in Supramolecular Copolymers Driven by Triazine–Benzene Interactions. *Chemistry - A European Journal, 29*(53), Article e202301726. https://doi.org/10.1002/chem.202301726

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DOI: 10.1002/chem.202301726

Document status and date:

Published: 21/09/2023

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.

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 The final published version features the final layout of the paper including the volume, issue and page numbers.

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Research Article doi.org/10.1002/chem.202301726

Hot Paper



Temperature Directs the Majority-Rules Principle in Supramolecular Copolymers Driven by Triazine–Benzene Interactions

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Dedicated to our distinguished colleague Professor Maurizio Prato and his seminal contributions to the science of functional materials.

Supramolecular copolymers have typically been studied in the extreme cases, such as self-sorting or highly mixed copolymer systems, while the intermediate systems have been less understood. We have reported the temperature-dependent microstructure in copolymers of triazine- and benzene-derivatives based on charge-transfer interactions with a highly alternating microstructure at low temperatures. Here, we investigate the temperature-dependent copolymerization further and increase the complexity by combining triazine- and benzene-derivatives with opposite preferred helicities. In this case, intercalation of the benzene-derivative into the triazine-derivative assemblies causes a helical inversion. The inversion of the net helicity was rationalized by comparing the mismatch penalties of the

Introduction

One of the most intriguing and unanswered questions in science is how homochirality emerged in nature. A hypothetical explanation for the origin of homochirality is the stochastic existence of a minor asymmetry in chiral systems, followed by an amplification mechanism towards enantiopurity.^[1-3] It is widely adopted that the amplification of asymmetry relies on the competition between opposite chiral entities as a result of their physical properties.^[4-8] In polymer science, extensive

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- Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202301726
- Special This article is part of a joint Special Collection in honor of Maurizio Prato.
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individual monomers, which indicated that the benzenederivative dictates the helical screw-sense of the supramolecular copolymers. Surprisingly, this was not reflected in further investigations of slightly modified triazine- and benzene-derivatives, thus highlighting that the outcome is a subtle balance between structural features, where small differences can be amplified due to the competitive nature of the interactions. Overall, these findings suggest that the temperature-dependent microstructure of triazine- and benzene-based supramolecular copolymers determines the copolymer helicity of the presented system in a similar way as the mixed majorityrules phenomenon.

investigation of the competition in helical and thus chiral polymers lead to the derivation of the Majority-Rules principle^[9] and the Sergeant-Soldiers principle.^[10] These principles were later translated to the field of supramolecular polymers, which provide the beneficial characteristic of forming highly dynamic structures.^[11,12] Numerous examples have been reported that demonstrate the sensitivity of supramolecular copolymers to small amounts of asymmetry in the system composition via strong amplification effects.^[13-18] Transfer of chirality from chiral carbon nanodots to porphyrin monomers was successfully demonstrated by Maurizio Prato and his group, which was amplified by supramolecular assembly of the porphyrins units.^[19] Most studies have been focused on helical supramolecular copolymers of two enantiomers, where nonracemic mixtures show a nonlinear helical bias in comparison to the enantiomeric excess. Although this approach can be insightful when studied across many samples at different mixing ratios, it is difficult to control the competition between the helical copolymers within each sample.

Recently, we reported a supramolecular copolymer system based on triazine- and benzene-centered monomers that showed a temperature-dependent copolymer microstructure with a highly alternating order at low temperatures.^[20] The comonomers had distinct homopolymerization properties: the triazine-centered monomer strongly aggregated in cooperative fashion at low concentrations (5–20 μ M) whereas the benzene-derivative only showed weak and less cooperative aggregation at much higher concentrations (>75 μ M). Nonetheless, the

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monomers copolymerized well due to the charge-transfer interactions between the two cores.^[21] Simulations with massbalance models provided details about the strength of the homo- and hetero-interactions and elucidated the temperaturedependent copolymer microstructure with a highly alternating sequence at low temperatures.^[22] With the interest to further explore this intriguing copolymerization, we studied the Ncentered analogues of triazine- and benzene-centered monomers to investigate the competition in helical copolymers from a new perspective.

For this purpose, two monomers with opposing preferred helicities were combined and the net copolymer helicity was monitored while varying the temperature. Applying computational methods to analyze the experimental data,^[22] we could relate the net copolymer helicity to the fraction of assembled comonomers. We found that the benzene-centered monomer wins the competition and dictates the copolymer helicity when equal amounts of these specific comonomers are copolymer-ized. The opposite helicity is only present at high temperatures, where the benzene-derivative does not yet participate in the polymerization, or in mixtures with a significant excess of the triazine-derivative. These findings enhance our fundamental understanding of competitions in supramolecular polymer systems, which might shed light on the origin of homochirality.

Results and Discussion

Homopolymerization of N-centered triazine and benzene derivatives

We synthesized and characterized the triazine-derivative S-T_N and benzene-derivative S-B_N with N-centered amide connections and chiral (S)-2,6-dimethylheptyl alkyl chains to introduce a helical bias in the supramolecular polymers. As a result, the supramolecular homopolymerization of $S-T_N$ and $S-B_N$ could be investigated with electronic circular dichroism (ECD) spectroscopy (Figure 1). In comparison to the previously reported analogues with C-centered amide connectivity,^[20] $S-T_N$ showed the same bias in helical screw-sense, and we could fit a massbalance model^[23] for cooperative polymerization to the cooling curves. In contrast, S-B_N surprisingly displayed the opposite preferred helicity of the C-centered amide analogue (Figure S1). Moreover, S-B_N precipitated at intermediate temperature (precipitation starts between 40 and 60°C at these experimental conditions) as indicated by the large linear dichroism (LD) signal, which was completely absent in the C-centered amide analogue under the same conditions. Because of the unexpectedly low solubility of S-B_N in the selected solvent mixture, decalin with 10% 1,1,2,2-tetrachloroethane (TCE), the investigation of the homopolymerization was challenging. To circumvent this problem, we continued with copolymerization of $S-B_N$ with $S-T_N$. The copolymerization with $S-T_N$ might increase the solubility of S-B_N, similar to solubilizing complexing agents used in drug formulation,^[24] and allow us to gain insights into the assembly properties of $S-B_N$ at the same time.

Copolymerization of N-centered triazine and benzene derivatives

Despite the opposing helical preference of the monomers, S- T_N -S-B_N mixtures still showed clear signs of copolymerization, notably with a gradual helical reversal when cooled from high to low temperatures (Figure 2a). The elongation temperature $(T_{\rm e})$ of the mixture was the same as the $T_{\rm e}$ of **S-T_N** homopolymers, which suggests that $S-T_N$ first polymerizes, and $S-B_N$ intercalates in the polymers at lower temperatures as demonstrated in the copolymerization of the C-centered counterparts. The mixtures were in thermodynamic equilibrium, as indicated by the overlapping heating- and cooling-curves (Figure 2b), thus we employed theoretical mass-balance models^[22] to determine the thermodynamic parameters of the assembly processes and investigate the copolymerization mechanism. For this purpose, we fitted the model to cooling curves of selected $S-T_N-S-B_N$ mixtures (Figure 2c). Using the extracted thermodynamic parameters of this copolymer system (Figure 2e), the same copolymerization mechanism was observed as in the previous report,^[20] where the triazine-derivative assembled at high temperatures and upon cooling the benzene-derivative intercalated into the supramolecular polymers (Figure 2d), forming a highly alternating microstructure (Figure S2 and S3). The shape of the cooling curves and the apparent mechanism show remarkable resemblance to our previous study of chiral monomers in chiral solvents,^[25] but now the comonomer participation, rather than the solvation, increases by lowering the temperature. The resulting competition between the different copolymer helicities is studied in detail by the simulations in the next paragraph.

Mixed majority-rules

Simulations of the competition between copolymer helicities over the studied temperature-range revealed that at high temperatures, mostly the preferred helicity of S-T_N was formed and upon cooling the majority was converted to the opposing helicity (Figure 3). The helicity of the $S-T_N-S-B_N$ copolymers followed the mixed majority-rules principle,^[26] as evident from the nonlinear relation between the compound excess and the net helicity (Figure 3d). Since $S-T_N-S-B_N$ mixtures showed a high dependency of the copolymer composition on the temperature, we could tune the compound excess in the copolymers simply by changing the temperature. At high temperatures, the copolymers contained mostly $S-T_N$ and at low temperatures an equal mixture of the two compounds was approached as a result of the preferred alternating copolymer composition. By simulating the net helicity and the compound excess within the copolymers in an equal mixture at different temperatures, a similar majority-rules plot could be constructed, although the shape was affected by the changing temperature and concentration of the assembled comonomers. In the majority-rules experiments described, a S-T_N excess of 0.1 equivalents was required to obtain a net helicity of 0, which indicated that S-B_N dictates the helicity in the mixed majority-rules experiments. Research Article doi.org/10.1002/chem.202301726 European Chemical Societies Publishing



Figure 1. a) Molecular structures of monomers $S-T_N$ and $S-B_N$, b) ECD spectra of 20 μ M $S-T_N$ in decalin/TCE (9/1 v/v) at 100 (red) to 0 (blue) °C, c) ECD (blue) and LD (red) spectra of 20 μ M $S-B_N$ in decalin/TCE at 20 °C, d) ECD cooling curves of 5 to 20 μ M $S-T_N$ in decalin/TCE, monitored while cooling from 105 to 0 °C at 1 K/min. Fit result of mass-balance model for cooperative polymerizations are displayed as continuous lines, experimental data as open circles. e) ECD cooling curves of 10 to 20 μ M $S-B_N$ in decalin/TCE, monitored while cooling from 75 to 5 °C at 1 K/min.

This implied that the mismatch penalty of $S-B_N$, which is the penalty to go into polymers with its unfavored helicity, was higher than the mismatch penalty of $S-T_N$ and that therefore it was more favorable for the copolymers to adopt the preferred helicity of $S-B_N$ instead of $S-T_N$. The expected higher mismatch penalty for $S-B_N$ was in line with the extracted thermodynamic parameters from the fitting of the mass-balance model.

As an attempt to rationalize the higher mismatch penalty, molecular modeling calculations of monomers and trimers were performed (Figure S4). The $S-T_N$ monomer showed a planar geometry, while $S-B_N$ adopted a propeller geometry with the

amides almost in plane with the adjacent aryl groups of the core. We then constructed trimers of $S-T_N$ in a *P*-helical arrangement and replaced the central $S-T_N$ monomer with $S-B_N$ monomers with either the *P*- or *M*-propeller geometry. We observed significant bending of the $S-T_N$ monomers in the trimer with the *M*-propeller and a planar geometry of $S-B_N$, while the *P*-propeller could be incorporated in the trimer, retaining both the propeller geometry of $S-B_N$ and the planarity of the $S-T_N$ monomers. These differences in the hetero-trimer structures might indicate that opposite propeller geometries

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Figure 2. a) ECD spectra of a mixture of 20 μ M *S*-**T**_N with 20 μ M *S*-**B**_N in decalin/TCE from 100 (red) to 0 (blue) °C, b) ECD cooling curves of 15 + 15 μ M *S*-**T**_N/*S*-**B**_N mixture (purple) in decalin/TCE, monitored while cooling from 105 to 0 °C at 1 K/min, c) ECD cooling curves of *S*-**T**_N/*S*-**B**_N mixtures in decalin/TCE, monitored while cooling from 105 to 0 °C at 1 K/min. C) ECD cooling curves of *S*-**T**_N/*S*-**B**_N mixtures in decalin/TCE, monitored while cooling from 105 to 0 °C at 1 K/min. Fit result of mass-balance model for copolymerizations are displayed as continuous lines, experimental data as open circles, d) Speciation of *S*-**T**_N and *S*-**B**_N in mixed samples, calculated from the thermodynamic parameters obtained via the fitting procedure, e) Thermodynamic parameters for supramolecular copolymerization, obtained from fitting procedure. Legend: (a) NP indicates the enthalpic nucleation penalty; (b) The cooperativity parameter specified is calculated at 20 °C; (c) MMP indicates the enthalpic mismatch penalty for a monomer to assemble in its unfavored helicity.

are unequally incorporated in helical supramolecular polymers of $S-T_N$, resulting in a higher mismatch penalty of $S-B_N$.

Mixed majority-rules of C-centered counterparts

To investigate if the higher mismatch penalty of the propellershaped core compared to the planar core is irrespective of the amide connectivity and the side chains, we performed a control experiment with the C-centered counterparts of the benzene and triazine-centered monomers R-B_c and S-T_c. The (S)- enantiomers were previously used in copolymerization, where the individual compounds adopted the same preferred helicity in the homopolymers. This copolymerization resulted in an increased ECD signal with the same sign. To study the mixed majority rules of these C-centered analogues, we synthesized the (*R*)-enantiomer of the benzene monomer. If this benzene monomer **B**_c also has the higher mismatch penalty than **T**_c, it is expected that the cooling curve of the mixture would show the same trend as in Figure 2b, with a helix inversion as a result of the mixed majority rules competition that is dominated by the benzene derivative. In contrast to the N-centered mixed Research Article doi.org/10.1002/chem.202301726



Figure 3. Simulated temperature-dependent distribution of monomers over copolymers with opposing helical screw sense for a) $S-T_{N'}$ b) $S-B_{N'}$ c) Sum of monomers. d) Net helicity of copolymers calculated as a function of the excess of polymerized $S-T_N$ monomers in comparison to $S-B_N$. The purple axes display the relation of this graph to the temperature and total concentration of assembled monomers. Simulations were performed on a $15 + 15 \mu M$ mixture of $S-T_N$ and $S-B_N$.

majority-rules system, the helix inversion was completely absent in the C-centered mixed majority-rules system and instead the ECD signal increased upon cooling. Only for large excesses of R- B_c , the system showed a helix inversion at low temperatures, indicating that S- T_c wins the mixed majority-rules competition and thus has the highest mismatch penalty. Obviously, the inverted amides do not only change the hydrogen-bonding in the polymers, but also affects the pK_a of the amides, the electron-density of the monomers and the position of the stereocenters in the side chains. Particularly the electron-density of the monomers is expected to drastically affect the copolymerization, which is dictated by the charge-transfer interaction between the benzene- and triazine-centered monomers. Therefore, it remains inconclusive what specific property of the monomers affects the mismatch penalty, and we still rely on copolymerization experiments to determine the outcome of competition between monomers.

Conclusions

In this work, we have investigated the helicity of temperaturedependent supramolecular copolymers. The competition between the triazine- and benzene-centered comonomers, which preferred the opposite helical handedness, resulted in an inversion of the copolymer helicity upon cooling. By combining spectroscopic techniques with computational methods, we could correlate this helix inversion with the temperaturedependent copolymer composition and show that the copolymer helicity followed the mixed majority-rules principle. At low Research Article doi.org/10.1002/chem.202301726



Figure 4. a) Molecular structures of monomers S-T_c and R-B_c, ECD cooling curves of b) 15+15 μ M (purple) and c) 5+5 μ M (purple), 5+25 μ M (cyan) S-T_c/R-B_c mixture in decalin/TCE, monitored while cooling from 100 to 10°C at 1 K/min.

temperatures, the copolymers approached an equal mixture of the two comonomers, adopting the helicity of the most dominant monomer. Supportive molecular modeling suggested that the propeller-shaped monomer overrules the planar monomer in the majority-rules competition due to the larger steric constraints of the propeller within the polymers. However, further experiments with slightly modified triazine- and benzene-derivatives did not confirm this general explanation and hence suggested that the competition is additionally influenced by other features of the comonomers. This underlines that it can be difficult to explain observed chirality in complex supramolecular systems and that additional control experiments are required to assess the generality of the preference of helicity in assembly of chiral molecules. Nonetheless, our findings showed that the asymmetry of supramolecular structures can be amplified non-linearly via co-assembly of structurally different components. We suppose that competitive processes in co-assemblies could be a general mechanism towards defined handedness in supramolecular systems, which might aid to elucidate the origin of homochirality in nature.

Experimental Section

Details on synthesis, characterization of synthesized molecules, additional UV-Vis and ECD spectra, details of the thermodynamic

model and molecular modeling results are provided in the Supporting Information.

Supporting Information

The authors have cited additional references within the Supporting Information.^[27]

Acknowledgements

We thank Bart Markvoort for fruitful discussions. The work received funding from the European Research Council (H2020-EU.1.1., SYNMAT project, ID 788618) and the Dutch Ministry of Education, Culture and Science (Gravitation Program 024.001.035).

Conflict of Interests

The authors declare no conflict of interest.

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Data Availability Statement

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

Keywords: Chirality · copolymerizations · copolymers superstructure · supramolecular · polymers

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Manuscript received: May 30, 2023 Accepted manuscript online: July 5, 2023 Version of record online: August 22, 2023