Future of Supramolecular Copolymers Unveiled by Reflecting on Covalent Copolymerization

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ABSTRACT: Supramolecular copolymers are an emerging class of materials, and in the last years their potential has been demonstrated on a broad scale. Implementing noncovalent polymers with multiple components can bring together useful features such as dynamicity and new functionalities. However, mastering and tuning the microstructure of these systems is still an open challenge. In this Perspective, we aim to trace the general principles of supramolecular copolymerization by analyzing them through the lens of the well-established field of covalent copolymerization. Our goal is to delineate guidelines to classify and analyze supramolecular copolymers in order to create a fruitful platform to design and investigate new multicomponent systems.

INTRODUCTION

While one-dimensional supramolecular polymers have long been employed by Nature as a powerful structural motif, scientists have only recently begun to exploit their dynamicity, directionality, and functionality. This confluence of properties makes them promising for applications in pharmaceuticals, nanoelectronics, and catalysis, but many fundamental principles that dictate the structure of supramolecular polymers remain unresolved. In 2009, we proposed to draw inspiration for future research directions by carefully considering the maturation of its older sister, covalent polymerization.† Following Carothers’s classic classification, we organized supramolecular polymers based on the process through which each aggregate is formed. Connections between the two fields became strikingly clear. Isodesmic polymerization can be considered a noncovalent analogue of step growth polymerization, characterized by high polydispersity and a degree of polymerization that depends on the association constant of the supramolecular units. Ring–chain supramolecular polymerization is similar to ring opening polymerization and depends on the equilibrium between linear and cyclic aggregates. Finally, cooperative supramolecular polymerization can be correlated to chain growth polymerization. This process is typically under thermodynamic control; although kinetically trapped copolymers are reported, over time such species generally convert into the thermodynamically most stable state. These connections helped to highlight the distinctions between covalent and supramolecular polymerization processes, rendering underlying research needs into tangible goals.

In this context, one of the directions that we identified was the intriguing challenge to make well-defined supramolecular copolymers. At that time, in contrast to the multitude of methods available to tailor covalent copolymers, there were few synthetic strategies to control the microstructure of supramolecular copolymers. The challenge is the inherent lability of noncovalent bonds, which are typically kinetically and thermodynamically less stable than covalent bonds. However, in the past ten years, considerable inroads have been made to reconcile the dynamics of supramolecular copolymers with the demand for microstructural control. Many studies and comprehensive reviews2–6 have since been published focusing on nucleation-elongation processes, kinetic control, competition, pathway complexity, and supramolecular monomer design.

Given the field’s nascent, we propose it is timely to critically reflect on recent progress through the lens of covalent chain copolymerization to illuminate challenges and opportunities for the future. Considering the ubiquity of well-defined covalent copolymers, we postulate that controlling the structure of one-dimensional supramolecular copolymers is paramount to realize next-generation functional materials. Our objective is to generate insight into urgent research directions by creating a strong link between covalent and noncovalent copolymerization worlds. The first supramolecular copolymers, such as the one reported by Lehn and co-workers,7 are based on an isodesmic mechanism and noncovalent interactions among complementary units, but in this work we mainly focus on cooperative chain growth processes. In isodesmic (step) copolymerization, the sequence of repeating units is either dictated by differing complementarity or randomized in the case of equal reactivity. For cooperative (chain) copolymerization, the challenges are similar to those of their covalent counterparts. As a point of reference, we chose to structure this work based on the organization employed in the chain copolymerization chapter of Odian’s classic textbook Principles of Polymerization.8 We focus on the classification and synthesis of state-of-the-art structures, discussing the parallel roles of direct characterization and theoretical models that are fundamental for the development of the field.

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SUPRAMOLECULAR CHAIN GROWTH COPOLYMERIZATION

Covalent and Noncovalent Copolymerization: Similarities and Differences. The mechanisms of covalent chain growth copolymerization and cooperative supramolecular (chain growth) copolymerization carry several similarities. At the outset of both processes, a certain activation is required to initiate polymer growth. For covalent polymers, a reactive initiator (e.g., a radical, cation, or anion) reacts with a monomer to generate an active propagating species that enchains additional monomers (Figure 1a). Similarly, supramolecular polymers require the generation of a nucleus (e.g., generally an energetically unfavorable small aggregate) to initiate the cooperative growth of a supramolecular copolymer (Figure 1b). Just as in covalent processes, the initiation and growth of supramolecular copolymers are sensitive to impurities, cosolvents, reaction time, and temperature. All these considerations dictate average molecular weight and microstructure. Just as in covalent copolymerization, changes to reaction conditions, and so we acknowledge the importance of solvent molecules as structural units. It is potentially misleading because it deemphasizes the concentration of each type of monomer sequence. However, excluding vitrimers and other reversible polymers, these changes are permanently encoded into the final covalent polymers. In the case of pathway complexity, as a consequence of the inherent dynamicity of supramolecular polymers, the concentration of each type of aggregate is not constant and responds to changes in reaction conditions. The ability to tune aggregated structures at will highlights the extreme sensitivity and potential utility of these structures.

Noninnocent Effect of Solvents in Supramolecular Polymerization. Before proceeding, it is important to consider solvent in defining copolymer compositions. In the case of covalent copolymerization, the choice of solvent can be an important tool for tuning relative polymerization rates, which ultimately determines the microstructure of a copolymer. The interaction between the solvent and the propagating polymer species is frequently supramolecular in nature. For example, solvent polarity dictates the strength of ion pairing in the anionic copolymerization of vinyl monomers, which modulates the reactivity of the propagating carbanion chain-end toward different monomers depending on their respective structures. The resulting polymers are then typically represented in terms of their polymerized monomer units. When dispersed in a solvent, the solvent interacts with the polymer to some degree depending on the temperature and the reactivities of the polymer and the solvent. However, these associated solvent molecules are generally not included in the polymer’s chemical structure because they are not covalently bonded to the polymer.

This distinction does not exist in the case of supramolecular copolymerization because solvent molecules interact with supramolecular copolymers via the same kinds of noncovalent forces that hold the monomers together. For this reason, a supramolecular “homopolymerization” of a single monomer may not be a homopolymerization at all. Solvent molecules could serve an essential role in supporting the fiber’s supramolecular structure, and thus such a naming convention is potentially misleading because it deemphasizes the microstructure of a copolymer. The nature of the bonds that hold supramolecular and covalent polymers together is sharply distinct. In contrast to the thermodynamic stability of covalent copolymers, supramolecular copolymers are dynamic because they are held together by comparatively weak noncovalent interactions (e.g., hydrogen bonding, π–π stacking, and van der Waal’s forces). The monomer sequence of a supramolecular copolymer is fluxional, as monomers can change their relative positions within a given polymer chain or integrate into other chains. Consequently, supramolecular polymers do not terminate in the way that covalent polymers do. These properties impart unique adaptability and modularity to the resulting materials, but they render the analysis of their structure a great challenge. Another striking difference is that supramolecular polymerizations often show pathway complexity. Small differences in the conditions of aggregation (e.g., variation in temperature or solvent) can cause a given set of monomers to form different self-assembled structures. Covalent polymerizations are also sensitive to changes in reaction conditions, giving rise to fluctuations in, for example, polydispersity, tacticity, and monomer sequence. However, excluding vitrimers and other reversible polymers, these changes are permanently encoded into the final covalent polymers. In the case of pathway complexity, as a consequence of the inherent dynamicity of supramolecular polymers, the concentration of each type of aggregate is not constant and responds to changes in reaction conditions. The ability to tune aggregated structures at will highlights the extreme sensitivity and potential utility of these structures.

Figure 1. Growth mechanisms for chain polymerization. (a) Covalent polymer activated by an initiator, which subsequently undergoes propagation or termination. (b) Supramolecular polymer formed by a cooperative mechanism, which is activated by the unfavorable formation of a nucleus and elongated by the favorable incorporation of additional monomers.

Perspective

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usually evaluated using circular dichroism spectroscopy, can be controlled through tuning the interplay of structure and reactivity between both the supramolecular polymer and the solvent. Our group and others have shown that the shape of the solvent can directly influence the helicity of supramolecular fibers, suggesting that molecular packing of solvent into the fiber’s corona gives rise to perturbations to the inner core of the fiber.
Water must also be acknowledged for its importance as a structural element in supramolecular polymers in bulk and in solution. In the bulk, Qi, Schalley, and co-workers demonstrated that water acts as an essential structural component that unlocks impressive adhesive properties of supramolecular polymers formed with crown ether-functionalized benzene tricarboxamides. In aqueous media, Han, Stupp and co-workers established a striking resemblance between the interaction of water and synthetic peptide nanofibers with the interaction between water and natural supramolecular materials such as proteins. Water in the interior of such fibers exhibit rapid diffusion, while water at the surface of the fiber is essentially immobilized, suggesting that these water molecules form hydrogen bonds with the fiber and serve an integral role in supporting the fiber’s structure. In organic solvents as well, several reports recently reported that the monomeric nature of water in alkanes gives rise to a potent thermodynamic driving force for it to bind to codissolved supramolecular polymers and effect profound changes to their structures. We postulate that this growing body of research expresses both the complexity and importance of solvent changes to their structures. We postulate that this growing body of research expresses both the complexity and import of solvent changes to their structures. We postulate that this growing body of research expresses both the complexity and import of solvent changes to their structures.

**Type of Copolymers.** Linear covalent copolymers are commonly categorized by the pattern of monomer enchainment. For example, for a polymer made up of monomers A and B, we can assign it as random, alternating, block, blocky, or periodic (Figure 2). Random copolymers do not have a regular pattern of monomer enchainment. Alternating copolymers, represented as poly(A-alt-B), contain the monomers in a regular alternating pattern. A related microstructure is periodic, which has the monomers sequenced in a regular pattern; for example, poly(A-per-B) indicates that two A monomers are enchained in a row followed by one B monomer. Block and blocky copolymers contain both long sequences of each monomers in the copolymer chain. Diblock copolymers, poly(A-b-B), are linear polymers with long sequences of each monomers, while multiblock (“blocky”) copolymers exhibit multiple short runs of each monomer in a given polymer. As presented in Figure 2c, we classify supramolecular structures using the same IUPAC formalism that is used for covalent polymers.

In the next sections, we critically review the theoretical tools and synthetic strategies for constructing well-defined one-dimensional structures. We shall consider the range of known microstructures and the limits of structural characterization. We focus especially on synthetic strategies and characterization challenges.

**SUPRAMOLECULAR COPOLYMER COMPOSITION**

As in covalent copolymerization, theoretical models are essential for understanding the composition of supramolecular copolymers. Theory is especially valuable here because the inherent dynamicity of supramolecular copolymers makes it difficult to experimentally determine microstructure. In the model developed by ten Eikelder and Markvoort, this behavior is accounted for by treating supramolecular copolymerizations as a set of reversible reactions between monomers and polymers. Similar to the terminal model of chain copolymerization, the equilibrium constant of a reaction is assumed to depend only on the identity of the last-enchainged monomer; an added assumption is that monomers can only add to the end of a growing chain. For example, the coassembly of A and B to form supramolecular copolymer P can thus be described by four reactions (Figure 3a) that provide the basis for deriving expressions for the concentration and composition of the copolymers.

The concentration of copolymers is expressed in terms of the concentration of polymerized monomer units ([M]_{pol}), which in turn can be expressed in terms of the total concentration of monomer ([M]_{tot}) and the concentration of free monomer ([M]_{free}, Figure 3b, top). A similar equation can be derived for the fraction of polymerized monomers \( \varphi_{pol} \) (Figure 3b, bottom). To determine the concentration of free monomer as well as the concentration and composition of the copolymers, the elaborated forms of these mass balance equations are solved numerically with the input consisting of the known [M]_{tot} and the experimentally determined equilibrium constants \( K_{A-B} \), \( K_{A-A} \), \( K_{B-B} \), \( K_{A-B} \), and \( K_{B-B} \) (Figure 3a).

From this model and subsequent fitting, we can extract thermodynamic parameters that help us to understand supramolecular microstructure. As in covalent copolymerization, reactivity ratios are a useful tool for comparing microstructures when the monomers are less, equally, or more reactive in copolymerization compared to homopolymerization. Here, the reactivity ratio \( R \) is defined as the ratio of Gibbs free energy change of the homoaggregation (\( \Delta G_{A-A} + \Delta G_{B-B} \)) to the Gibbs free energy change of the heteroaggregation (\( \Delta G_{A-B} + \Delta G_{B-A} \)). Figure 3c. For values of \( R \) greater than unity, monomers preferentially interact with their own type of monomer, while for values of \( R \) smaller than unity, the monomers tend to coassemble.

This behavior is reflected in the shape of the copolymerization curve obtained for each class of \( R \). As an example, we simulated the results for the temperature-induced supramolecular copolymerization of A and B. We arbitrarily set the thermodynamic parameters such that the elongation temperatures for poly(A) and poly(B) are 60 and 70 °C, respectively. We then varied the value of \( R \) by keeping the values of \( \Delta G_{A-A} \) and \( \Delta G_{B-B} \) constant and modifying the values of \( \Delta G_{A-B} \) and \( \Delta G_{B-A} \). In this way, we modulate the tendency of the monomers to interact with each other while holding their tendency to homopolymerize constant. The resulting copolymerization curves (shades of gray), as well as the fraction of polymerized A and B (red and blue, respectively), are presented in Figure 3d. As \( R \) approaches infinity, two elongation temperatures are clearly evident, consistent with self-sorted homopolymerization of A and B. As the value of \( R \) is reduced, only one elongation temperature is evident, suggesting some degree of copolymerization. This elongation temperature shifts toward higher temperatures as the value of \( R \) is decreased; that is, the copolymer forms at higher temperature as heteroaggregation becomes more favorable. The incorporation of A and B in poly(A-co-B) depends on \( R \) as well. A coinciding incorporation of the two monomers is visible for alternating systems (\( R < 1 \)) whereas increasing the value of \( R \) results in a greater disparity between the red and blue curves.

A useful extrapolation is the calculation of the fraction of polymerized \( A, F_A \), as a function of temperature (Figure 3e,f). For \( R > 1 \) (black curve), at high temperatures, the copolymers are rich in monomers of type A. As temperature decreases, monomers of type B enter into the copolymers, and the composition of the copolymers approaches the composition of the mixture of monomers. For \( R < 1 \) (lightest gray curve), where alternating structures can be formed, at high temperatures
monomers B are already incorporated into the copolymers and the copolymers’ composition already resembles the composition of the mixture. Thus, as the value of $R$ decreases, monomers enter into the copolymers more by interacting with the other type of monomer and less by interacting with their own type of monomers.

An important issue to keep in mind, as with all models, is that care must be taken to evaluate the validity of the assumptions for the system at hand. This model strictly considers the interactions between two monomers in a fully reversible system—complications due to solvent interactions, pathway complexity, and kinetic traps are excluded. In cases where such factors strongly influence self-assembly, one can either modify the model to account for new interactions or use the base model without fitting to generate simulations for qualitative comparison.

### MICROSTRUCTURE OF COPOLYMERS

#### Sequence-Length Distribution. For the sake of simplicity, the average copolymer microstructure is usually discussed. However, as indicated by the terminal model for covalent copolymerization and the thermodynamic model presented above for supramolecular copolymerization, the composition of a given copolymerization, and thus its precise microstructure, changes as a function of conversion. For covalent copolymers, small changes in microstructure can have important implications for their properties. This challenge was a key motivation to develop sequence-controlled copolymerization such that the monomer sequence can be unambiguously controlled throughout the copolymerization. Interestingly, this issue has a different meaning in the context of supramolecular copolymers because of their dynamicity. The inter- and intrachain exchange of monomers tends to homogenize the composition for all copolymer chains in a given system.

Despite a growing number of strategies to achieve new supramolecular copolymer microstructures, unambiguous structural determination persists as a key challenge in supramolecular copolymerization. In this case, the monomers’ exchange and the intrinsic dynamicity complicate the characterization of the microstructure. There are several outstanding reports of supramolecular copolymers that provide strong evidence for alternate, sequenced and block microstructures; we critically review them here and use them as a guide to reconsider some seminal works where the microstructure determination was not possible.

#### Alternating Copolymers. Alternating supramolecular copolymers were the first category of supramolecular copolymers reported. In 1990 Lehn and co-workers presented seminal works on 1D poly(A-alt-B) structures based on multiple hydrogen-bonded complementary units. Other examples of isodesmic copolymerization using complementary units and organometallic supramolecular systems have since been reported by several groups. Another common structural motif exploits donor-acceptor monomers that copolymerize via charge transfer interactions. Evidence of copolymerization is primarily accomplished by demonstrating the inability of each monomer to homopolymerize.

More recently, Besenius and co-workers demonstrated alternating supramolecular copolymers in aqueous solutions and by sequential growth from Au-surface. Monomers based on benzene tricarboxamides bearing positively charged $\beta$-sheet encoded oligopeptides form alternating copolymers poly(1-alt-2) via electrostatic interactions (Figure 4a). Another example of peptide assembly has been reported by Giuseppone’s group. Copolymerization in water between bisurea domains functionalized with bioactive peptide or fluorescent cyanine dyes resulted in fibers with an alternated fashion as established by fluorescence experiments. Working instead in the bulk, Araki and co-workers in 2003 reported the formation of alternating supramolecular copolymers between cyclohexane tricarboxamides functionalized with linear and bulky side chains. The bulky monomer could not form stable homopolymers, but the authors found that it copolymerizes with the less bulky monomer in an alternating fashion based on infrared spectroscopy.

An interesting example reported by Li and co-workers relies on hierarchical organization to form an alternating supramolecular copolymer (Figure 4b). They employ zinc porphyrins that aggregate via complementary hydrogen bonding to form the hexamer ($3_c$). This assembly is geometrically compatible to react with the hexadentate monomer 4. The authors use a combination of spectroscopic and static light scattering techniques to show that the monomers arrange in an alternating fashion to produce poly[$(3)_c$-alt-4].

#### Periodic Copolymers. Few examples of sequenced supramolecular copolymers have been reported. Wüthner’s group...
described in 2009 the formation of poly(A$_2$-per-B) structured copolymers via unconventional interactions between complementary monomers: a perylene bisimide ($\text{6}$) and an azobenzene-functionalized melamine ($\text{5}$, Figure 5a). They reported that $\text{5}$ and $\text{6}$ do not form long organized structures in methycyclohexane (MCH) in a 1:1 ratio as expected for ditopic 3-folded hydrogen bonding complementary units. Contrarily, the polymerization with a 2:1 ratio of $\text{5}$-$\text{6}$ unexpectedly formed a periodic copolymer poly[(5)$_2$-per-$\text{6}$] with J-type aggregation. The authors stressed the importance of the assembly protocol to achieve organized structures, as it required an equilibration time of 15 h at 20 °C. Atomic force microscopy (AFM) shows the presence of tightly coiled helical polymers with defined pitch (6 nm) and length (100–200 nm).

The Würthner group more recently reported how a related distorted perylene bisimide bearing imides protected with water-soluble chains (8) copolymerizes with a planar analogue (7) to form poly[(7)$_2$-per-$\text{8}$] (Figure 5b). The homopolymerization of $\text{7}$ in water follows a 1:1 mechanism to form stiff short nanorods via $\pi-\pi$ interaction; in contrast, $\text{8}$ forms dimers that aggregate into nanoworms via hydrophobic interactions. The copolymer is obtained under kinetic control by injecting water in a tetrahydrofuran (THF) solution of dissolved $\text{8}$ and $\text{7}$ in a 1:2 ratio, followed by the evaporation of the THF under ambient conditions. They assign the structure through a combination of optical microscopy, nuclear magnetic resonance (NMR) spectroscopy and transmission electron microscopy (TEM). Interestingly, poly[(7)$_2$-per-(8)$_2$] forms long and thin flexible fibers that deviate from the morphology of the two homopolymers, evidently because the combination of the flexibility of the dimers of $\text{8}$ and the rigidity of the 7-based blocks. This behavior is reminiscent of covalent elastomers where soft and hard blocks alternate to give new function.$^{70}$

**Block Copolymers.** Stitching covalent polymers together to form diblock and multiblock copolymers gives rise to properties that are more than the sum of their parts. The key to their function is their ability to microphase separate into hierarchical nanostructures, which is a function of the compatibility and the volume fraction ratio of the blocks. The promise of higher order structural control has motivated supramolecular chemists to create analogous supramolecular block copolymers. Again, the noncovalent nature of the bonds and the inherent difficulty to characterize such structures render this goal a great challenge.

Seminal works have exploited kinetic control to retard exchange dynamics enough to furnish supramolecular block copolymers via sequential addition of monomers. In 2007, Winnik, Manners and co-workers reported the synthesis of supramolecular triblock copolymers of the form poly(A-b-B-b-A) using poly(ferrocenyldimethylsilane) (PFS) block copolymers as the supramolecular monomeric units.$^{71}$ By a kinetically controlled process that they named living crystallization, they were able to create short cylindrical homomicelles that exhibit uniform growth upon the addition of more monomer. They achieved the triblock architecture with control over the lengths of the blocks through the addition of a different dissolved PFS monomer. These aggregates are stable over time because of their low dynamism. In contrast to the high dispersity observed for most supramolecular polymers produced through a cooperative mechanism, these structures exhibit low dispersity because of the “living” nature of this process, which was convincingly proven through TEM, static and dynamic light scattering (SLS, and DLS).

Research on PFS-based block copolymers has since flourished. Recent examples include the formation of regular crossed micelles,$^{72}$ di- and triblock comicles,$^{73}$ fluorescent multiblock micelles,$^{74,75}$ comicles between linear and brush units,$^{76}$ photoreponsive systems,$^{77}$ and multidimensional micelles.$^{78-80}$ Other types of monomer have been found to also undergo living crystallization, including poly(p-phenylenvinylene)$^{81}$ and poly(di-n-hexylfluorene)$^{82}$ The latter, based on electron poor (9) and electron rich (10) poly(di-n-hexylfluorene)s, copolymerizes to form poly(10-b-9-b-10), which exhibits long-range exciton transport (Figure 6a).

Pavan, Takeuchi, Sugiyasu, and co-workers$^{83}$ recently demonstrated a seeded-growth copolymerization strategy to create kinetically stable supramolecular block copolymers. They generate seeds by sonicating homopolymers of zinc-based porphyrin 11, and these seeds can be used to again grow poly(11) by adding additional 11 or to produce poly(12-b-11-b-12) by adding the copper porphyrin 12 (Figure 6b). This process yields aggregates with a predictable length based on the monomer/seed ratio along with a narrow polydispersity. Remarkably, the triblock copolymer exhibits greater stability toward the presence of a denaturant compared to the poly(11) homopolymer. Molecular dynamics simulations reveal that monomer exchange only occurs at the end groups of the

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Figure 5. Examples of periodic supramolecular copolymers achieved with different strategies. (a) Stable helical copolymers are obtained by unconventional hydrogen bonding interaction between complementary units of melamine-functionalized azobenzene 5 and perylene bisimide 6 resulting in poly[(5)$_2$-per-$\text{6}$]. (b) Planar 7 and twisted 8 perylene bisimides copolymerize under kinetic control to form long copolymers poly[(7)$_2$-per-(8)$_2$].
polymer, suggesting that the more stable poly(12) end blocks compartmentalize and protect the poly(11) midblock.

Another exceptional example is presented by Aida’s group, who reported the block copolymerization of hexabenzacoronenes based-monomers through sequential steps (Figure 6c). The bipyridine-terminated hexabenzacoronene units (13) homopolymerize in methanol to give bundles of poly(13). Metalation of the pendant bipyridine units with copper results in a dispersion of charged assemblies poly(13*-b-14). These aggregates are then dispersed in acetone and fragmented by sonication to create seeds. Upon adding 14 and cooling from 50 to 25 °C, the seeds initiate the supramolecular polymerization of 14 to give a mixture of diblock and triblock copolymers, poly(13*-b-14) and poly(14-b-13*-b-14), respectively.

Similarly to the synthesis of covalent block copolymers, the majority of supramolecular block copolymers are produced via a kinetic approach in which supramolecular polymers with low dynamicity can be fed with different monomers to form block structures. Their thermodynamic stability is in most cases limited, though. In contrast to these reports, we prepared supramolecular multiblock copolymers under thermodynamic control with tripyridylamine tricarboxamide 15 and triphenylamine tricarboxamide 16. We found that supramolecular multiblock copolymers poly(15-co-16) are produced both by directly mixing the homopolymers poly(15) and poly(16) and also by copolymerization of the molecularly dissolved monomers via a cooling procedure (Figure 6d). By combining optical spectroscopy and microscopy with the theoretical model developed for two-component supramolecular polymerization,
we were able to identify the microstructure of the polymer, finding that the block length distribution is closely related to the enthalpy of cointeraction of the different monomers with respect to the enthalpy of the related homointeraction.

**Random and Unresolved Structures.** Some of the earliest studies in the field of one-dimensional supramolecular polymerization consist of copolymerization experiments. Inspired by the work of Green and co-workers58–85 on helical covalent polymers, these experiments were designed to probe the amplification of chirality in helical one-dimensional supra-

molecular polymers. Typical experiments include mixing enantiomers of a monomer together (majority rules experi-

ment),88–92 mixing achiral monomers with chiral enantiopure analogues (sergeants and soldiers experiment),90,93–103 and mixing chiral enantiopure monomers in different ratios with an achiral counterpart (diluted majority rules experiment).104–106

The monomers in these cases typically comprise identical cores and only differ in the structure of their side chains. The mixtures were predominantly characterized using spectroscopic measurements such as fluorescence, ultraviolet–visible (UV–vis) spectroscopy and especially circular dichroism (CD). Apart from some notable exceptions,107 very few studies have corroborated the spectroscopic results with other types of characterization techniques. Usually, a stochastic incorporation of the monomers during the copolymerization process is assumed, but it has been difficult to experimentally assess if monomer incorporation is indeed fully random. Interestingly, several supramolecular copolymer systems exhibit a linear response in optical activity as a function of c.e. (majority rules) or percentage of chiral sergeant added (sergeant and soldiers). This lack of chiral amplification is a useful indicator for self-sorting (Figure 2), as it points to helical supramolecular homopolymers coexisting rather than mixing into copolymers. Detailed investigations by the groups of Wu and only di-

versely, recent developments in super resolution techniques. If applicable, TEM has proven to be an excellent tool to unravel structure.84 Otherwise, recent developments in super resolution fluorescence microscopy demonstrate that it can be helpful in unravelling polymer growth,118 dynamics,119 and structure.120–122 Furthermore, hydrogen–deuterium exchange followed by mass spectrometry is a valuable tool for following the dynamics of supramolecular systems in water.123,124

What is striking from these seminal works is the lack of a leading experimental technique to unambiguously determine a copolymer’s structure and the consequent need to bridge this gap with a combination of multiple techniques. This situation differs from that of covalent copolymers, where 1H and 13C NMR spectroscopy are the primary tools for microstructural

The growing interest in developing noncovalent copolymers requires parallel progress and standardization of characterization techniques. As discussed above, such uniformity remains elusive. Other established fields, such as covalent copolymers, teach us that having a systematic, universally applied characterization routine is crucial to achieve concrete progress. However, the dynamism of supramolecular polymers and the noncovalent nature of the bonds between the monomers render microstructural analyses extremely challenging. Nevertheless, nowadays a clear trend on the supramolecular homopolymers characterization routine has emerged. The prevalent strategy combines spectroscopic measurements (especially useful for variable temperature or variable solvent measurements), microscopy (the most used are AFM, TEM, cryoTEM, and super resolution fluorescence microscopy), mass spectrometry, and light scattering techniques. These experimental techniques are complemented with molecular dynamics simulations and thermodynamic mass-balance models.

The outstanding reports on supramolecular copolymers in which a detailed structure analysis is reported,80,84,116 adapt and combine these techniques to resolve the supramolecular copolymer microstructure. Spectroscopy measurements (UV, CD, fluorescence, etc.) are powerful tools to unravel both the copolymerization mechanism and composition of a given system by quantifying changes in spectroscopic features. Thereafter, spectroscopic results can be used in combination with theoretical modeling to predict the microstructure and the relative stability of the copolymer with respect to the homopolymers.50,117 The theoretical microstructural analysis can then be corroborated with judicious use of microscopy techniques. If applicable, TEM has proven to be an excellent tool to unravel structure.84 Otherwise, recent developments in super resolution fluorescence microscopy demonstrate that it can be helpful in unravelling polymer growth,118 dynamics,119 and structure.120–122 Furthermore, hydrogen–deuterium exchange followed by mass spectrometry is a valuable tool for following the dynamics of supramolecular systems in water.123,124

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determination. We believe that further studies for developing techniques which allow similar analyses for supramolecular analogues are needed and will permit more efficient growth in the field. Microscopy, modeling, and molecular dynamics simulations have so far resulted in promising strategies. More progress in these directions could lead toward the possibility of analyzing in detail the subtle structural details of supramolecular copolymers.

■ APPLICATIONS AND FUTURE PERSPECTIVES

The development of covalent copolymers has proven to be invaluable with time. Covalent copolymerization has opened the door to creating materials with properties simply not achievable with homopolymerization or blending. Considering supramolecular copolymers in this framework, we can dream of the advancements achievable through mastering dynamic multi-component structures. Their properties are particularly well suited for managing complexity through adaptability. For biological applications, the prospect of including multiple units, such as sensors, bioactive molecules, and catalysts, in a defined order in noncovalent systems would be a breakthrough for synthetic biosystems that require cooperative feedback between multiple systems. The same effects can be exploited in organic electronics where tuning the arrangements of dynamic copolymers would optimize the optoelectronic properties of, for example, photoelectronic switches, sensors and chiral devices. This Perspective is meant to initiate a cooperative effort to advance this new and promising field. Despite the great progress achieved in the last years, much more must come. We believe that the field of supramolecular copolymerization needs comprehensive growth spanning strategic molecular design to the exploitation of theoretical models to the development of powerful characterization techniques. Achievable through collaboration and standardized analytical routines, these efforts will bring supramolecular copolymers to be essential in cutting edge technology markets.

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