Secondary Structure in Nonpeptidic Supramolecular Block Copolymers

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CONSPECTUS: Proteins contain a level of complexity—secondary and tertiary structures—that polymer chemists aim to imitate. The bottom-up synthesis of protein-mimicking polymers mastering sequence variability and dispersity remains challenging. Incorporating polymers with pre-defined secondary structures, such as helices and π-π stacking sheets, into block copolymers circumvents the issue of designing and predicting one facet of their 3D architecture. Block copolymers with well-defined secondary structure elements formed by covalent chain extension or supramolecular self-assembly may be considered for localized tertiary structures.

In this Account, we describe a strategy toward block copolymers composed of units bearing well-defined secondary structures mixed in a "plug and play" manner that approaches a modicum of the versatility seen in Nature. Our early efforts focused on the concept of single-chain collapse to achieve folded secondary structures, either through hydrogen bonding or quadrupole attractive forces. These cases, however, required high dilution. Therefore, we turned

to the Ring-Opening Metathesis Polymerization (ROMP) of [2.2]paracyclophane-1,9-dienes (pCpd), which forms conjugated, fluorescent poly(*p*-phenylenevinylene)s (PPV) evocative of β-sheets. Helical building blocks arise from polymers such as poly(isocyanide)s (PIC) or poly(methacrylamide)s (PMAc) containing bulky, chiral side-groups while the coil motif can be represented by any flexible chain; we frequently chose poly(styrene) (PS) or poly(norbornene) (PNB). We installed moieties for supramolecular assembly at the chain-ends of our "sheets" to combine them with complementary helical or coil-shaped polymeric building blocks.

Assembling hierarchical materials tantamount to the complexity of proteins requires directional interactions with high specificity, covalent chain extension, or a combination of both chemistries. Our design is based on functionalized Reversible Addition-Fragmentation Chain-Transfer (RAFT) agents that allowed for the introduction of recognition motifs at the terminus of building blocks and chain-terminating agents (CTA) that enabled macroinitiation of helical polymers from the chain-end of ROMP-generated sheets and/or coils. To achieve triblock copolymers with a heterotelechelic helix, we relied on supramolecular assembly with helix and coil-shaped building blocks. Our most diverse structures to date comprised a middle block of PPV sheets, parallel or antiparallel, supramolecularly- or covalently-linked, respectively, and end-functionalized with molecular recognition units (MRUs) for orthogonal supramolecular assembly. We explored PPV sheets with multiple folds achieved by chain extension using alternating pCpd and phenyl-pentafluorophenyl β-hairpin turns. Using single molecule polarization spectroscopy, we showed that folding occurs preferentially in multi-stranded over double-stranded PPV sheets. Our strategy towards protein-mimicking and foldable polymers demonstrates an efficient route toward higher ordered, well-characterized materials by taking advantage of polymers that naturally manifest secondary structures. Our studies demonstrate the

retention of distinct architectures after complex assembly, a paradigm we believe may extend to other polymeric folding systems.

Key References

- Elacqua, E.; Croom, A.; Manning, K. B.; Pomarico, S. K.; Lye, D.; Young, L.; Weck, M. Supramolecular Diblock Copolymers Featuring Well-Defined Telechelic Building Blocks. *Angew. Chem., Int. Ed.* **2016**, *55*, 15873-15878.[1] *Single-handed telechelic helical polymers as well as telechelic sheets and coils, assembled through complementary hydrogen bonding or metal coordination.*
- Pomarico, S. K.; Lye, D. S.; Elacqua, E.; Weck, M. Synthesis of Sheet-Coil-Helix and Coil-Sheet-Helix Triblock Copolymers by Combining ROMP with Palladium-Mediated Isocyanide Polymerization. *Polym. Chem.* **2018,** *9*, 5655-5659.[2] *Termination of ROMP-generated diblock copolymers with a palladium-functionalized vinyl ether allowed for chain extension with isocyanides.*
- Elacqua, E.; Manning, K. B.; Lye, D. S.; Pomarico, S. K.; Morgia, F.; Weck, M. Supramolecular Multiblock Copolymers Featuring Complex Secondary Structures. *J. Am. Chem. Soc.* **2017,** *139*, 12240-12250.[3] *The engineering of complex protein-mimicking polymeric structures requires methods for installing functional groups at both chain-ends, a toolbox of orthogonal supramolecular and covalent interactions, and methods for monitoring self-assembly.*
- Elacqua, E.; Geberth, G. T.; Vanden Bout, D. A.; Weck, M. Synthesis and Folding Behaviour of Poly(*p*-phenylene vinylene)-Based β-Sheet Polychromophores. *Chem. Sci.*

2019, *10*, 2144-2152.[4] *Incorporation of turns by sequential polymerization in between sections of conjugated, sheet-like polymers led to compact, folded structures.*

Introduction

Envisioning and assembling a puzzle without prior knowledge of how the pieces fit together requires creativity and an interdisciplinary approach. For example, the design of vast tubular structures—supramolecular polymers—calls for prediction of directional intermolecular interactions and hierarchical assembly in order to choose the repeat unit.[5] Similar challenges complicate the strategy of producing structures inspired by natural biomolecules, which contain perfect sequence specificity in addition to intricate assembly governed by directional interactions. The levels of protein hierarchy, from primary to quaternary structure, represent wide areas for the development of new chemistry emulating this biological order, including sequence-controlled polymerizations, site-specific polymer folding, self-assembly, self-replication, and catalysis.[6]

Techniques such as supported polymerization, protection/deprotection, and multi-component reactions are significant milestones toward achieving Nature's sequence specificity.[7] These advances, along with the greater number of synthetic monomers compared to natural amino acids, suggests that synthetic chemistry may even have the potential to surpass Nature's variety. Secondary and tertiary structure, the next levels in protein hierarchy available for synthetic mimicking, generally manifest in polymers and oligomers with a moderate level of sequence control (such as judicious tuning of block length) by incorporation of supramolecular interactions or covalent bonding sites to direct folding.[6] Certain non-amide-based homopolymers contain secondary structures as a consequence of steric restrictions or electronic interactions

between repeat units. The Weck laboratory's approach to generate complex, biologically-inspired materials utilizes polymers with main-chains reminiscent of proteinic secondary motifs, including α-helices, β-sheets, β-hairpins, and random coils (Figure 1).

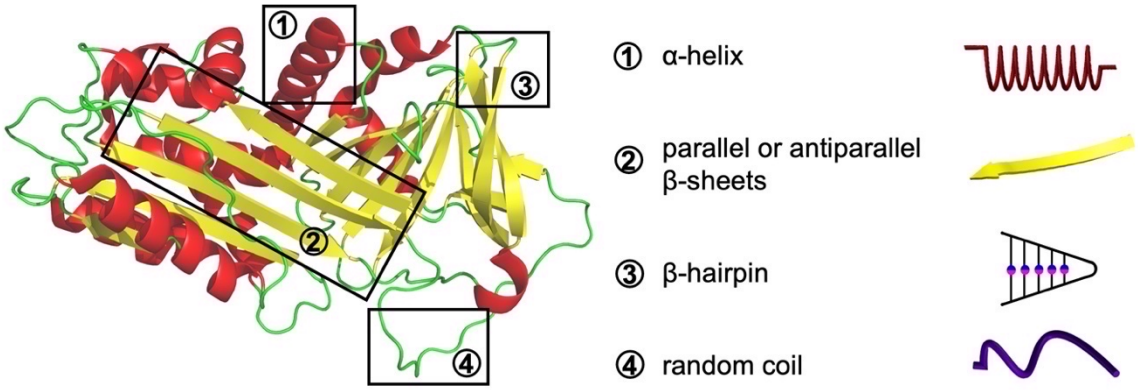

Figure 1: We select secondary structural elements found in protein ensembles to design and synthesize fundamental analogues using non-amide-based building blocks. Representative protein is a protease inhibitor (pdb: 3CWM) displayed in cartoon mode in PyMOL.

Design Strategy

Proteins fold because their compact conformations are thermodynamically stable in biological media.[8] While it may seem daunting to reproduce the plethora of biomacromolecular functions in synthetic polymers, Samuel Gellman pointed out over twenty years ago that the limitation may only be in human imagination.[9] At that time, scientists had just begun using Nature as a template for folding oligomers, or foldamers, and no true synthetic tertiary structures had been achieved. Tremendous advances in synthetic tertiary structures,[6] polymer sequence specificity,[7] and repertoires of structural elements for the next generation of nanosized materials[10] over the past two decades justify Gellman's remark.

In this Account, we describe our efforts to ascertain supramolecular bonding, identify new methods of supramolecular block copolymer assemblies, and elucidate higher order structures of Nature-mimicking materials. We turn to the diversity of biological systems for ideas on structure/function relationships. The α-helix, for example, may display structural heterogeneity, such as amphipathic helices,[11] or assembly, seen in coiled-coils,[12] and provides hints for new monomers or supramolecular approaches. Biology also provides us with ample ideas for future techniques and characterization methods and to translate our design for usage in aqueous conditions analogous to biological systems. Ironically, proteins can retain their 3D shape in certain organic solvents, albeit with limited catalytic ability, and modulation of the aqueous:organic solvent ratio reveals information about protein folding[8] (often referred to as a "paradox")[13] that may offer inspiration for elucidating the structures of our systems.

The Weck laboratory's approach to Nature-inspired structures utilizes secondary structure-containing organic polymers well-known in the literature, circumventing folding complications while allowing us to observe the interplay of different, well-defined macromolecular elements (Figure 2).[3] We use helical poly(isocyanide)s (PIC) and poly(methacrylamide)s (PMAc) to mimic α-helices and π-π stacking poly(*p*-phenylenevinylene)s (PPV) as synthetic analogues to β-sheets.[1, 14] We connect these telechelic/heterotelechelic elements by covalent bonds (through macroinitiation) or supramolecular chemistry, specifically, the complementary molecular recognition units (MRUs) of barbiturate (Ba) and Hamilton Wedge (HW) and/or the metallosupramolecular palladium(II) sulfur-carbon-sulfur (SCS) pincer complex/pyridine (Pin-Pyr) pair.[2, 15, 16] This use of multiple, orthogonal assemblies in a single system enables programmable, stepwise assembly of complex structures.[17] In order to prepare well-defined polymers with predesigned molecular weights and low dispersities, we apply an

array of controlled polymerization techniques, including Ring-Opening Metathesis Polymerization (ROMP), Atom-Transfer Radical Polymerization (ATRP), Reversible Addition-Fragmentation Chain-Transfer (RAFT) polymerization, and palladium-catalyzed isocyanide polymerization. Incorporating quantitative functional end-groups, we strategically apply functionalized initiators, chain-terminating agents (CTA), and chain-end modification.[1-3, 16]

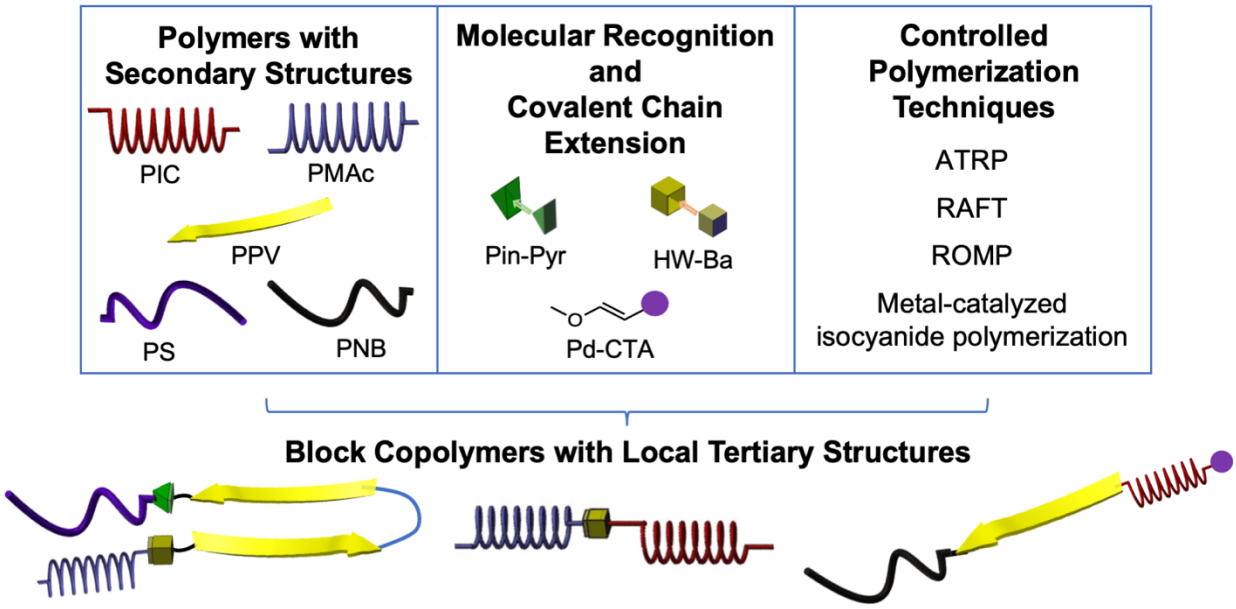

Figure 2. Synthetic polymers achieve local tertiary structures through the connection of secondary structure-bearing building blocks by supramolecular recognition units and/or covalent chain extension.[1-4, 14-16]

Helical Polymers

The unique conformation of helical biopolymers stimulates chemists to create synthetic analogs, including polymers, peptidic foldamers, helical aromatic amides, arylene ethynylene foldamers, and others.[18, 19] The inherent chirality, originating from the backbone of synthetic helical polymers, finds application in building blocks for macromolecular architecture design and

holds great potential for complex materials.[20, 21] Helical polymers can be divided into two categories according to their helical inversion barriers.[22] One category is characterized by a high helix inversion barrier greater than 85 kJ/mol, and includes poly(isocyanide)s (PIC), poly(methacrylamide)s (PMAc), and poly(methacrylate)s. For these static helical polymers, the development of a preferred handedness requires polymerization of monomers featuring chiral and bulky moieties or the use of chiral catalysts.[22] The second category, characterized by low inversion barriers, features dynamic helical polymers including poly(isocyanate)s, poly(acetylene)s, and poly(silane)s.[22] In these materials, incorporation of only a small amount of chiral monomer or the use of an optically active initiator can induce a preferred handedness ("sergeants and soldiers" effect).[23] Noncovalent interactions between dynamically racemic helical polymers and small chiral molecules can also induce an excess of helical sense.[24]

PICs and PMAcs (Figure 3a) became our building blocks for α-helices for constructing well-defined macromolecular architectures due to their wide synthetic scope of monomers and stable helices. Less studied in the literature than PICs, the naphthyl-based PMAc maintains its helix by intramolecular hydrogen bonding and steric repulsion of chiral pendant groups.[25] As for PICs, bulky side-chains induce approximately four repeat units per turn.[26] Common catalytic systems for the polymerization of isocyanides include transition metal complexes. Nickel(II) catalysts are the most widely used and versatile for most isocyanides while palladium complexes are mainly used for the polymerization of aromatic isocyanides (Figure 3b).[27] Atomic force microscopy [28] and transmission electron microscopy (TEM) allow for direct visualization of the helix and its handedness.[29, 30] PICs with alanine-based side-chains synthesized by the Nolte group feature well-ordered internal hydrogen bonding networks; β-sheets upon helices.[31] Using amino acid-based or aromatic PICs, morphologies such as vesicles or spherical nanoparticles can

be observed.[32-34] Further applications of helical polymers take advantage of their inherently asymmetric backbone-induced environment that creates sites for chiral recognition and asymmetric catalysis.[35, 36]

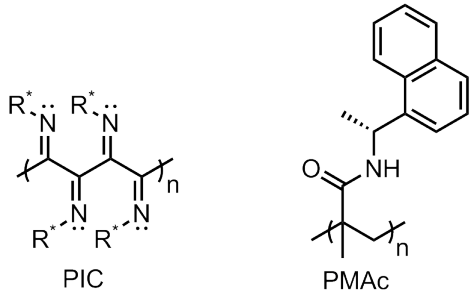

Figure 3. Poly(isocyanide)s (PIC) maintain helical, single-handed secondary structure through steric repulsion between bulky, chiral R* groups and nitrogen lone pairs.[26] Hydrogen bonding between amides and steric repulsion of chiral naphthyl groups induces helicity in poly(methacrylamide)s (PMAc).[25]

Single Strand Collapse: Nanoparticles and Turns

Single-chain nanoparticles (SCNPs) mimic Nature by folding/cross-linking a polymer chain into a compact structure. Cross-linking strategies include noncovalent interactions, metal coordination, and light-triggered assembly.[6, 37] SCNPs that emulate protein folding can be used as catalytic nanoreactors, contrast agents for biological imaging, and vehicles for drug delivery.[6, 37] With regards to the synthesis of SCNPs, the interchain cross-linking and the potential for intrachain side-reactions limit the scale of most procedures to very low concentrations (< 1 mg/mL) and frequently stymies characterization by NMR spectroscopy.[6] SCNPs represent a class of polymers that encompasses, to some extent, all levels of protein-inspired hierarchy, though Barner-Kowollik argues that for the time being they do not possess true secondary

structure.[6] Some of the highest levels of order in SCNPs include tadpole shaped polymers[38] as well as hydrogen bonding stacks of benzene-1,3,5-tricarboxamide (BTA) units (Figure 4a).[39] These stacks arrange vertically into a helix, reminiscent of the biological motif, while HW and cyanuric acid (CA) blocks drive further compaction. β-Sheets and β-hairpins also represent a wide opportunity for Nature-inspired synthesis, from the approaches of polymer chain folding and scaffold methods.

Early attempts at engineering peptidomimetic β-hairpins relied on rigid aromatic scaffolds or various small molecules to direct folding of peptide strands.[40, 41] More recent scaffolds depend on small molecules bearing orthogonal functional groups for the appendage of polymers. Binder and coworkers applied a bicyclic carbohydrate-based β-turn mimic, incorporating both an azide and carboxylic acid, to orthogonal "click" chemistry and amidation reactions with two different heterotelechelic poly(isobutylene)s. This controlled assembly of an artificial, hydrophobic β-sheet was sterically challenging due to the proximity of the two reactive moieties (Figure 4b).[42] As opposed to using small molecule β-turn scaffolds, our group realized polymeric β-hairpin structures by single-chain folding for easy incorporation into block copolymers.

One of our earlier attempts towards β-hairpin-type polymer relied on quadrupole interactions between phenyl and pentafluorophenyl groups (Figure 4d). In this case, sequential RAFT of styrene, *N*,*N*-dimethylacrylamide, and pentafluorostyrene produced a folding triblock copolymer.[43] In a later study, similar to some of Barner-Kowollik and Meijer's SCNPs,[39] we incorporated hydrogen-bonding units into a polymer backbone to drive single-chain folding. We appended ureidoguanosine (UG) or diaminonaphthyridine (DAN) pendants (complementary MRUs) to norbornenes for ROMP and included a flexible, aliphatic norbornene middle block to

produce a two-stranded β-sheet (one β-turn) under dilute conditions (Figure 4c).[44] Both of our β-hairpins possess certain advantages; the UG-DAN macromolecular folding polymer contains stronger noncovalent interactions while the phenyl-pentafluorophenyl triblock does not interfere with other hydrogen bonding motifs that may be present in a larger system. For the latter reason, we used quadrupolar interaction-based β-hairpins in our larger assemblies that also contain Ba/HW pairs (Figure 4e). Although we referred to the UG-DAN polymer as a "sheet," we later settled on a toolbox of secondary structure-containing polymers and use the term "sheet" to only refer to π-π stacking poly(*p*-phenylenevinylene)s (PPV).

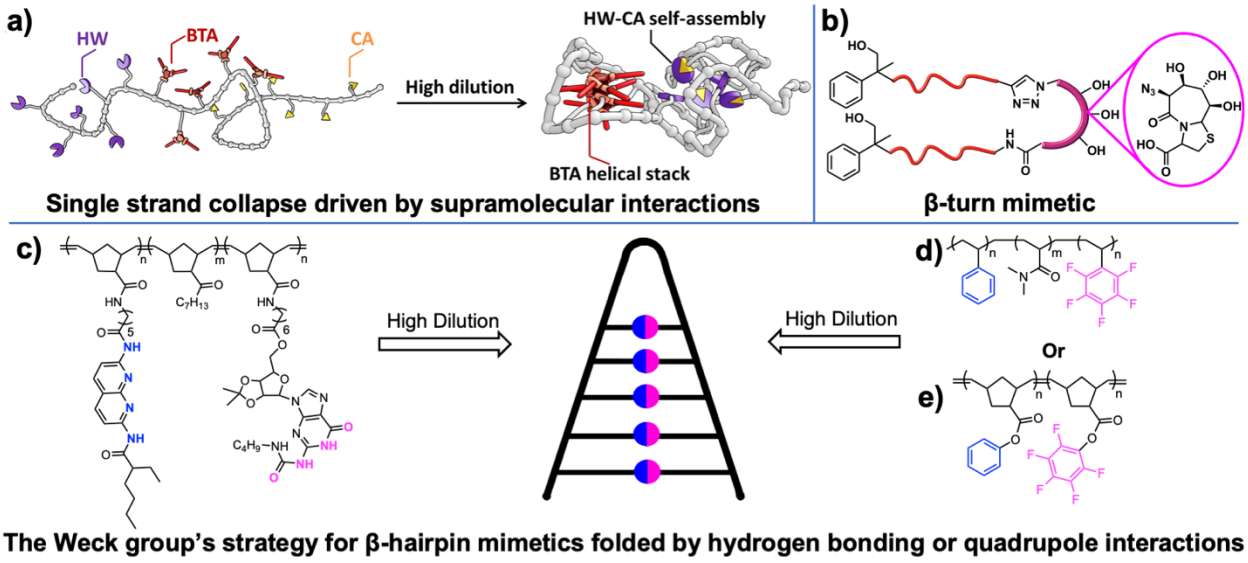

Figure 4. (top) (a) Single strand collapse that leads to single-chain nanoparticles (SCNPs) folded by local supramolecular assemblies. (b) A bicyclic carbohydrate-based β-turn mimetic. (bottom) Our strategy of making β-hairpin mimic structures through single-chain folding driven by ureidoguanosine (UG)-diaminonaphthyridine (DAN) hydrogen bonding (c) or quadrupole interactions (d and e). Figures 4a and b reproduced with permission from refs 40 and 43. Copyright 2015 ACS and 2014 ACS, respectively.

β-Sheet-Mimicking Structures and Poly(p-phenylenevinylene)s

β-Strand and β-sheet biomimicry have long been attempted for peptidomimetic applications such as enzyme inhibitors and molecular recognition.[45, 46] β-Sheet-mimicking small molecules and foldamers fall into two major classes: aromatic and aliphatic (though the latter may still feature aromatic moieties). Both classes utilize inter- and/or intramolecular hydrogen bonding to realize sheet alignment. Rigidification may be achieved by π-conjugated systems, such as terephthalamide, while their alignment is orchestrated by hydrogen bonding.[47, 48] Zhao and co-workers reported an oligo(*p*-phenylene ethynylene) (OPPE) sheet with alternating side-chains of amides and esters allowing for intramolecular hydrogen bonding between the chromophores. These noncovalent interactions between the OPPE sheets afforded a narrowed band gap due to an extended conjugation length.[45] Despite the abundance of oligomeric and foldameric β-sheets, polymeric sheets are rare.

While our β-sheet design that relied on single chain folding was successful, the strategy is limited to a single β-turn. Artificial β-sheets containing additional β-turns have only been achieved using face-to-face π-π interactions of aromatic moieties strategically held in place by β-hairpin motifs. Huc and co-workers reported a multi-stranded β-sheet composed of aromatic oligoamides forming up to four β-turns (five β-strands) using an iterative synthesis.[49, 50] The advantages of applying this scaffold motif to a polymer-based strategy include simple incorporation of complexity either during the synthesis of the monomer or from the polymerization phase.

For a polymeric β-sheet, we looked to conjugated polymers that could be synthesized in a living fashion and settled on PPV, a conjugated polymer with a rigid delocalized structure.

Grubbs and coworkers formed PPVs using ROMP of bis(carboxylic ester) derivatives of bicyclo[2.2.2]octadiene followed by a thermally induced elimination under harsh conditions to form the desired unsubstituted PPV.[51] In 1958, Cram and coworkers first reported [2.2]paracyclophane-1,9-dienes (pCpd), the highly strained cyclic compound whose strain energy was later found to be greater than 40 kcal mol^{-1}.[52, 53] For soluble alkyl and alkoxy substituted PPVs, the Turner group developed a straightforward synthesis of substituted pCpds and their living ROMP[54, 55] which can be easily monitored using ^{1}H NMR spectroscopy affording soluble polymers with low dispersity, ideal for our purposes.

Following the Turner group's synthesis, we synthesized alkoxy-substituted PPV blocks as bio-inspired β-sheets and demonstrated their folding.[4] Using functionalized Grubbs initiators has allowed for easy integration of functionality at one polymer terminus during the initiation step while functionalized CTAs append various groups to the other chain-end resulting in a heterotelechelic polymer.[56] Our current PPV sheets have advantages over our predecessor UG-DAN polymer as it allows for the fabrication of single-stranded and multi-stranded sheets in a single step.

Synthesis of Block Copolymers with Pre-Determined Secondary Structure

Supramolecular Assembly and Covalent Chain Extension to Form Diblock Copolymers

Prior to our work, supramolecular block copolymer strategies encompassed diverse structures,[57] however, few utilized helical blocks in polymeric assemblies. In 2016, we demonstrated the first helix-helix supramolecular block copolymer.[14] We used a functionalized palladium initiator and a RAFT agent with supramolecular recognition motifs to obtain telechelic helical polymers with high end-group fidelity. A HW-functionalized PIC and a Ba-functionalized

PMAc assembled into a diblock copolymer through hydrogen bonding with an association constant of (9.5 ± 0.5) × 10^3 M^{-1} as characterized from ^{1}H NMR spectroscopic titration of the two polymer blocks, monitoring the imide N-H_c protons of Ba-PMAc and the amide N-H_a protons of HW-PIC (Figure 5a and b). The association constant compared well to the association constants of the two helical building blocks with complementary small molecule partners and the known value for the HW/Ba pair (K_a = 10^4 – 10^5 M^{-1} in $CHCl_3$).[14, 58] In natural biomolecules, rigid helices maintain their structure in a chaotic milieu, hence, we found it promising that our diblock copolymers retained their distinct helical conformations upon supramolecular assembly, as evidenced by circular dichroism (CD) and IR spectroscopy.

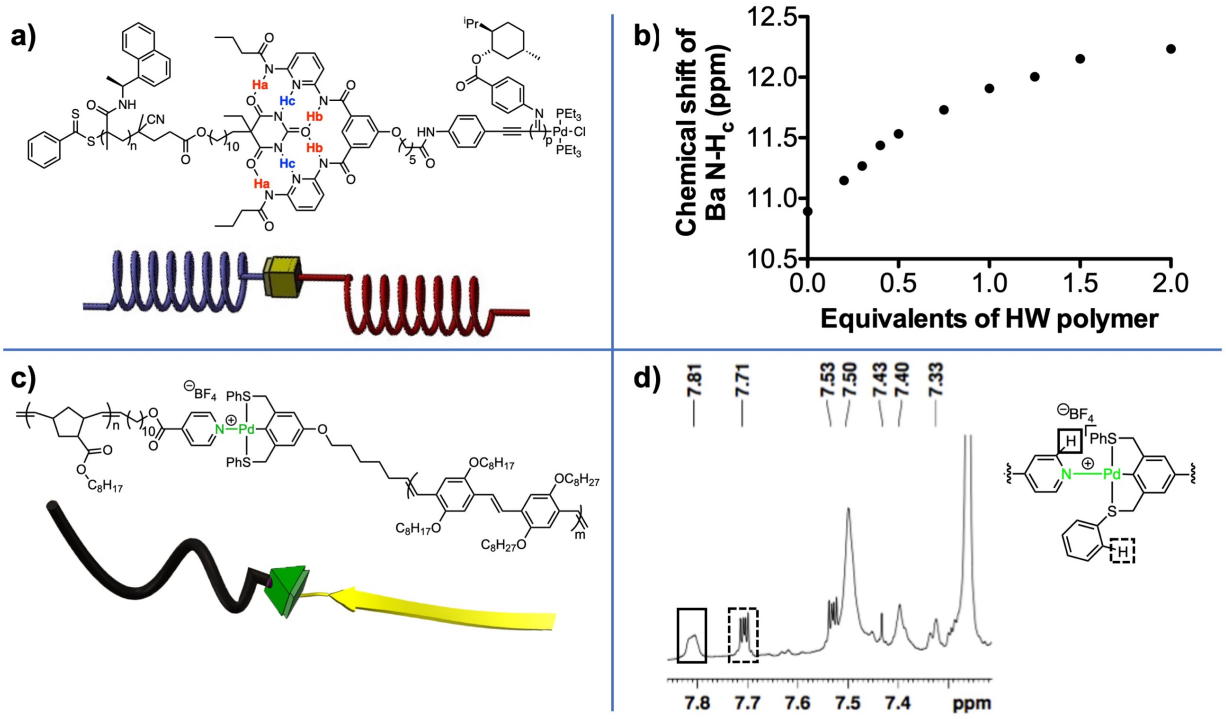

Figure 5. Selected supramolecular diblock copolymer assemblies and representative experimental results: (a) Helix-helix diblock copolymers assembled by hydrogen bonding. (b) ^{1}H NMR titration of Ba and HW containing polymers tracking the assembly process ($CDCl_3$, 500

MHz, 25°C). (c) A coil-sheet diblock copolymer assembled through metal coordination and (d) partial ^{1}H NMR spectrum highlighting the metal coordination ($CDCl_3$, 600 MHz). Figures 5b and d adapted with permission from refs 14 and 1. Copyright 2016 ACS, 2016 Wiley, respectively.

The supramolecular helix-helix block copolymer proved the concept of assembling polymers with distinct secondary structures through end-functionalized MRUs. Apart from telechelic helical polymers, we expanded the library of building blocks by introducing coil-like poly(norbornene)s (PNB) and poly(styrene)s (PS), as well as sheet-like PPVs. We reported four sets of supramolecular diblock copolymers; two sheet-helix structures with different helical blocks assembled by the Ba-HW MRUs as well as coil-helix and coil-sheet through the Pin/Pyr metal coordination (Figure 5c and d).[1] ^{1}H NMR spectroscopy tracked the successful assembly of all four diblock copolymers. Sheet-like PPVs typically formed lamellar morphologies in the solid state with several characteristic wide-angle X-ray scattering (WAXS) diffractions: inter-backbone alkyl-alkyl chain interdigitation (d ~ 18 Å, 2θ ~ 4.5°), π-π stacking (d ~ 4.5 °A, 2θ ~ 20°), and intra-backbone monomer repeat units (d = 6.2 °A, 2θ = 14.3°).[1] We observed only minor differences among the sheet diblock copolymers, suggesting that PPV segments largely maintain their original features in the supramolecular assemblies.

In order to expand our toolbox of protein-mimicking architectures, we considered an essential element of natural biomolecules—primary structure—which exists as a series of covalent bonds. Hence, utilizing covalent bonds between our secondary structure-containing blocks allows for sturdier linkages rather than solvent-dependent hydrogen bonding. We applied a macroinitiation strategy to overcome common challenges associated with covalent block copolymer constructions, including monomer compatibility, insufficient yields and purification

problems.[59, 60] In particular, we employed ROMP to make PNB coils or PPV sheets, followed by quenching with a palladium-functionalized vinyl ether (Figure 6a). The resulting palladium end-group-functionalized polymers serve as macroinitiators for the polymerization of menthol isocyanides, resulting in coil-helix or sheet-helix diblock copolymers (Figure 6b).[15] GPC demonstrated a clear shift to higher molecular weights after polymerization of the isocyanide (Figure 6c).

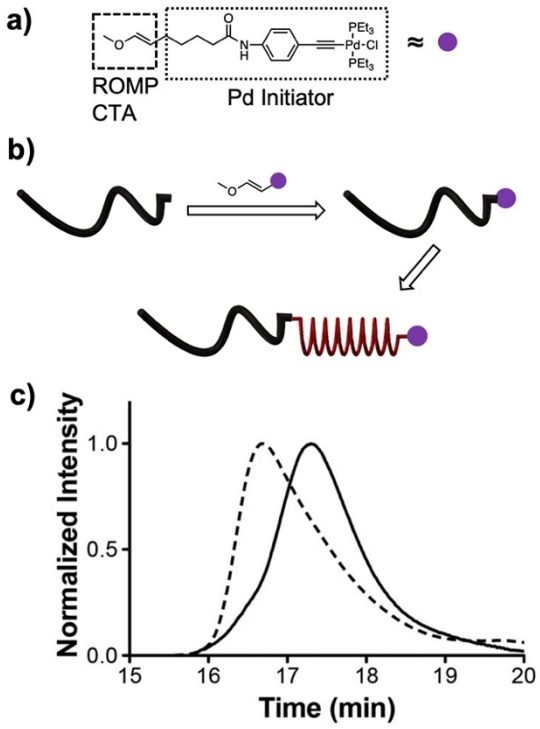

Figure 6. (a) A palladium-functionalized vinyl ether chain-terminating agent (CTA). (b) The CTA creates a macroinitiator for further fabrication of the coil-helix diblock copolymers. (c) GPC trace showed increased molecular weight upon chain-extension (bold: coil block; dashed: coil-helix diblock). Reproduced with permission from ref 15. Copyright 2017 Wiley.

Increasing Complexity: Triblock Copolymers

Incrementally moving closer towards complex, biologically-inspired materials, we extended the diblock strategy to triblocks by utilizing the living nature of ROMP to extend the chain with a second monomer in the same pot (Figure 7a).[2] Chain-end modification with a palladium-functionalized vinyl ether was followed by the palladium-catalyzed polymerization with menthol isocyanide. We easily changed the sequence of the ROMP blocks to yield sheet-coil-helix or coil-sheet-helix structures. The appearance of Cotton effects upon formation of the triblock copolymers confirmed incorporation of the helical segment (Figure 7b).

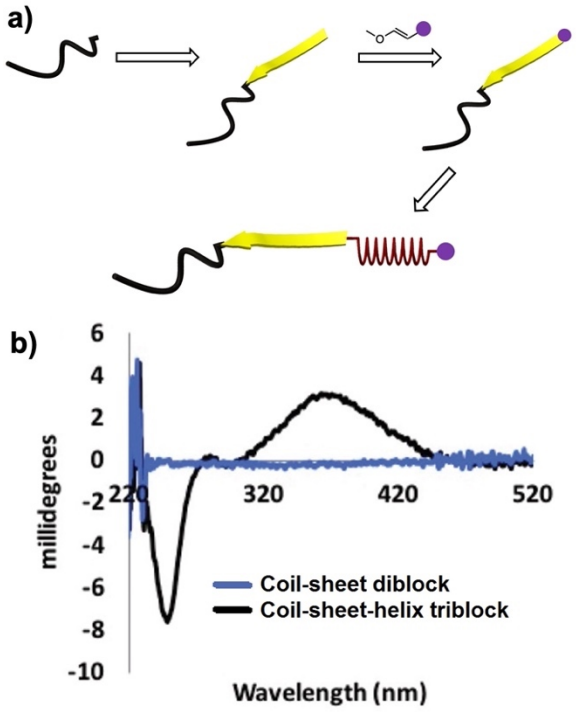

Figure 7. (a) Macroinitiation strategy for the construction of covalent triblock copolymers. The purple sphere on the vinyl ether represents a palladium catalyst that initiates the polymerization of aryl isocyanides. (b) The helical block retained its single-handedness in the block copolymer, as evidenced by the CD spectrum ($CHCl_3$). Adapted with permission from ref 2. Copyright 2018 Royal Society of Chemistry.

While the covalent approach produces materials that are resistant to cleavage under mild conditions, the modular supramolecular strategy allows for stimuli-responsiveness, as we observed in triblock copolymers without secondary structure.[61] The supramolecular "plug and play" approach, however, requires novel heterotelechelic middle blocks of both helices and sheets for optimum versatility. Percec,[62] Lowe and Davis,[63] and Binder[64] studied thio-halogen "click" reactions for the functionalization of RAFT-based polymers. We performed a thio-halogen "click" reaction on a polymer prepared by RAFT with a Ba-functionalized RAFT agent to attach a pyridine-bearing α-bromoester.[16] Together with HW-PIC and Pin-PS, we used this heterotelechelic helical PMAc to fabricate a supramolecular coil-helix-helix triblock copolymer. Specific viscometry increased from homoblock to triblock copolymers, confirming the assembly of the three segments (Figure 8).

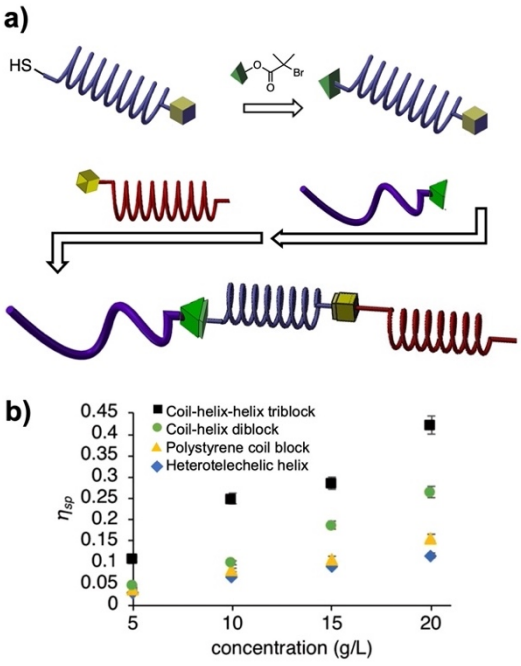

Figure 8. (a) A supramolecular coil-helix-helix block copolymer. The heterotelechelic helical middle block is key to the triblock copolymer formation. Sequential addition of complementary

building blocks yields the final materials. (b) The specific viscosity increases upon adding new blocks proved the successful assemblies ($CHCl_3$, 25°C). Reproduced with permission from ref 16. Copyright 2019 Royal Society of Chemistry.

Putting it all Together: Sheets, Helices, Coils, and β-Turns

In order to perform supramolecular assemblies with heterotelechelic sheets, we synthesized a HW-functionalized Grubbs II initiator (Figure 9a).[3] We terminated the ROMP polymerization of pCpd with Pin-or Pyr-functionalized vinyl ethers. We synthesized what we termed "parallel" β-sheet PPVs by the supramolecular assembly of Pin-PPV with Pyr-PPV. This double-stranded PPV contained HW units at both ends, which allowed for subsequent supramolecular assembly. We also sought to increase the complexity of our system by introducing turns into the β-sheet-mimicking polymers. This "antiparallel" strand contained a covalently attached β-hairpin with the phenyl-pentafluorophenyl stacking complex.[43] HW-functionalized Grubbs II initiator first polymerized a section of pCpd, followed by chain extension with equimolar amounts of phenyl norbornene (PNB) and pentafluorophenyl norbornene (PFP), followed by another section of pCpd terminated by Pin or Pyr vinyl ethers. We assembled the parallel and antiparallel sheets with other telechelic polymer blocks and produced several multiblock copolymers, including helix-parallel sheet-helix and helix-antiparallel sheet-coil (Figure 9a). We confirmed the assembly by the signature proton shifts in the ^{1}H NMR spectra of the formed supramolecular binding motifs, increases in viscosity of the multiblock copolymers, and decreases of the diffusion coefficient obtained from diffusion ordered spectroscopy (DOSY). Despite the increasing bulk of these multiblocks compared to previous diblock and triblock copolymers, the helicity of the PMAc and PIC blocks remained intact. This validates our design principle for protein-inspired block copolymers.

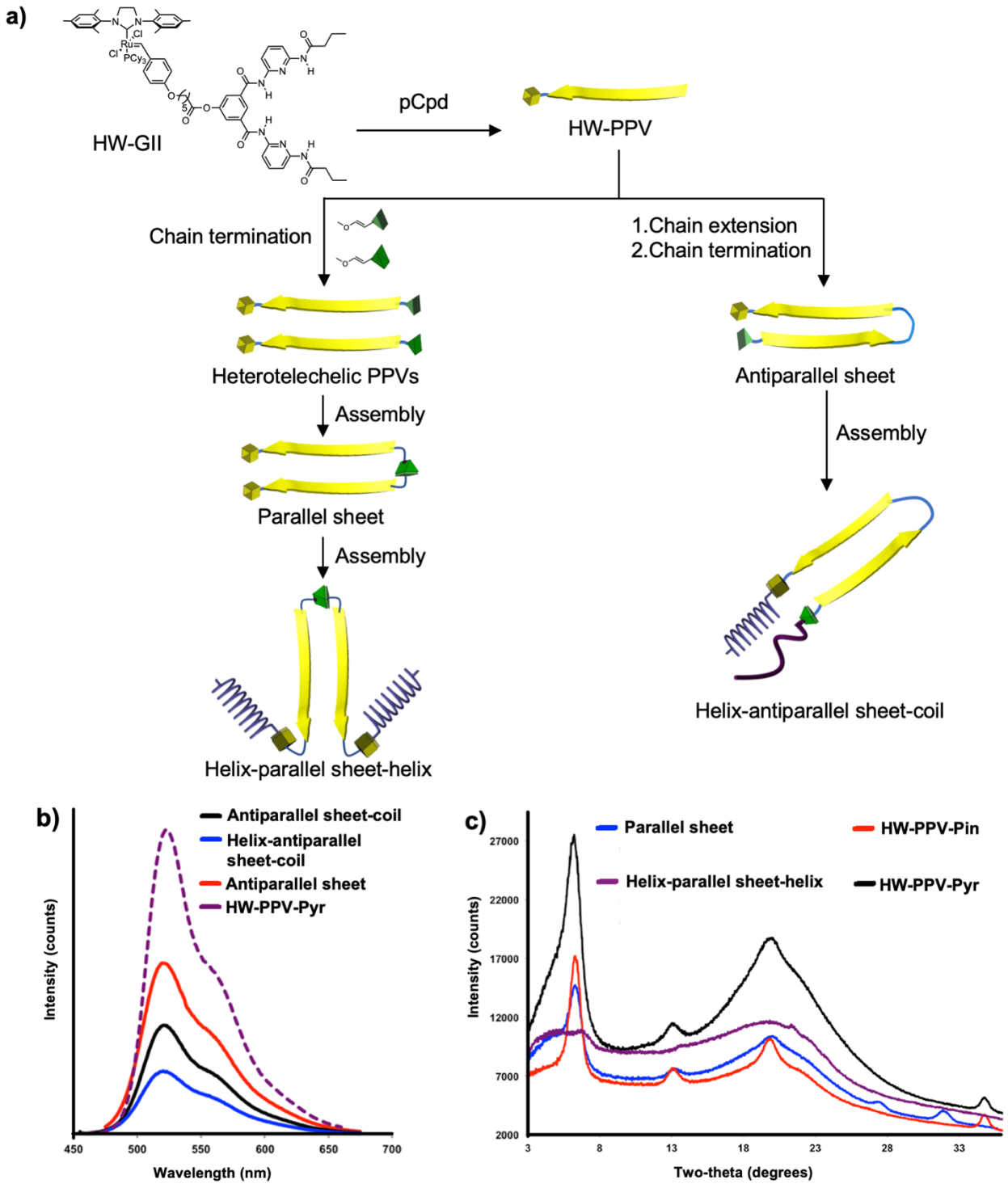

Figure 9. (a) Supramolecular multiblock copolymers featuring parallel and antiparallel PPV sheets synthesized using ROMP with a Hamilton Wedge-functionalized Grubbs initiator. (b) WAXS diffractogram of helix-parallel sheet-helix copolymer (purple) showing a leveling

between the intensities of the diffractions related to alkyl-alkyl interdigitation and π-π stacking. (c) The fluorescence emission intensities (λ_{ex} = 450 nm, $CHCl_3$) of supramolecular block copolymers decrease upon helix-antiparallel sheet-coil assembly (blue). Adapted with permission from ref 3. Copyright 2017 ACS.

Folding of Multiblock Sheets

Compartmentalization of sheets hinges upon breaking up the π-π stacking-induced aggregation of PPVs. Extensive studies on PPVs with regards to their emissive properties enumerated complex behaviors, such as blue to red phase transitions, core-shell aggregation, side-chain dependent suppression of aggregation, and folding.[65-68] In order to better probe the folded structure of antiparallel PPVs, we synthesized a series of antiparallel sheets, (PPV-b-PNB-b-PFP-b-)$_n$PPV, with up to n = 5, by iterative ROMP (Figure 10a and b).[4] Single molecule polarization spectroscopy provided an average measure of chromophore alignment. The population of single molecule conformations of the PPV homopolymer displayed larger spread than that of the 1-5 turn folded sheets, suggesting that the PNB-PFP turns, on average, lead to more frequent chromophore alignment. Furthermore, summing up an ensemble of single molecule emission spectra for every polymer revealed that PPVs with turns reproduce the bulk fluorescence spectrum, while the homopolymer contains variation in the position of the emission maximum (Figure 10c). Variation arises from differing conjugation length and conformation; hence, the folds of the higher order polymers instill a larger degree of order. Furthermore, we observe no change in the 0-0 to 0-1 transition intensity, suggesting a low degree of π-π stacking-induced aggregation.

The shape of these ensemble spectra compares well to bulk fluorescence spectra of the supramolecular sheet diblock, triblock, and tetrablock copolymers (Figure 9b). We also observed a significant decrease in fluorescence intensity for helix-parallel sheet-helix and helix-antiparallel sheet-coil structures (Figure 9b) compared to the un-assembled PPV homopolymer (HW-PPV-Pyr, Figure 9b). Knowledge gained from the single molecule excitation studies suggests that intrachain alkyl-alkyl interdigitation maintains folded PPV sheets in ordered conformations that preclude extensive π-π interactions, and thus, fluorescence quenching. If we can compare a quasi-solid state technique to solution properties, the observed decrease in fluorescence intensity for most of the supramolecular sheet assemblies seems to suggest the disruption of alkyl-alkyl interactions and heightened aggregation-induced quenching. The nature of the aggregation remains unclear, however, since H-aggregates typically feature a decrease in the intensity of the 0-1 transition relative to the electronic origin.

WAXS data corroborate the results from the single molecule polarization studies. The intensity of the peak corresponding to alkyl-alkyl interactions at low 2θ values increased from PPV-(PNB-PPV) to PPV-$(PNB\text{-}PPV)_5$, relative to the π-π stacking diffraction at high 2θ (Figure 10d). This observation agrees with the model of heightened intra-chain alkyl-alkyl interdigitation in longer, multi-folded sheets maintaining a better degree of separation between the phenylene aromatic surfaces. Homopolymers of PPV also display a higher proportion of alkyl-alkyl interactions compared to π-π stacking by WAXS (Figure 9c). Upon addition of one antiparallel turn, this alkyl-alkyl peak decreases (though the PNB-PFP block also contains a broad Bragg reflection in the same area as the PPV π-π stacking peak, around d = 4.7 Å). It would appear that one antiparallel turn induces a decrease in inter-chain interdigitation in the solid state while the addition of subsequent turns establishes a hierarchy of intra-chain interactions that impede

aggregation. Supramolecular assembly of antiparallel and parallel sheets with helices or coils, on the other hand, displayed a decrease in the intensities of reflections corresponding to alkyl-alkyl interdigitation relative to π-π stacking, albeit with significant broadening of all peaks (Figure 9c). The WAXS results add validity to our design principle for bio-mimicking block copolymers since supramolecular assembly and/or addition of phenyl-pentafluorophenyl hairpins drives compartmentalization of PPV strands.

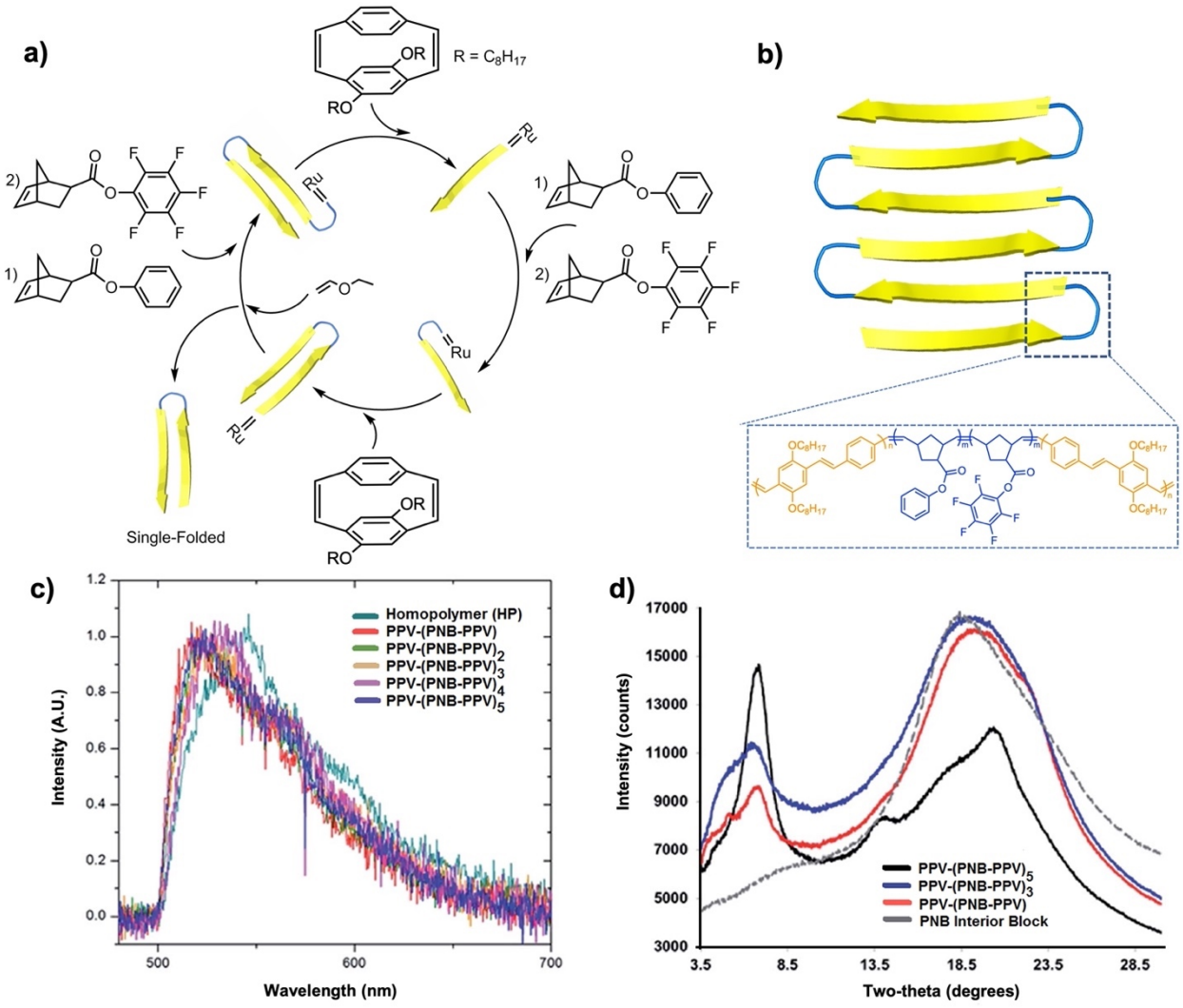

Figure 10. (a) Synthesis of antiparallel PPV sheets with one or more turns via ROMP using phenyl-pentafluorophenyl interactions to fold hairpin loops. (b) A 5-turn PPV sheet. Single

molecule ensemble fluorescence spectra (c) of the series of turn-containing PPVs maintain greater homogeneity than the homopolymer. The heightened diffraction (d) at $d \sim 18$ Å, $2\theta \sim 4.5°$, suggests better octyl chain-interdigitation for PPV-(PNB-PPV)$_5$ compared to PPV-(PNB-PPV). Adapted with permission from ref 4. Copyright 2019 Royal Society of Chemistry.

Conclusion

The structural fidelity of Nature's biomacromolecules derives, in part, from a molecular machine, the ribosome, which engineers perfect sequence specificity in every strand. Without such a tool, we turn to other features of biomacromolecules that enable them to catalyze, organize, and build the components of life – directional supramolecular interactions, hydrophobic pockets, incorporation of inorganic co-factors, and above all, the tenet that structure equals function. We drew inspiration from these structures comprising helices, sheets, coils, and β-turns to create our library of synthetic, Nature-mimicking constructs.

Prior to our work with secondary structure containing-polymers, we developed a toolkit of directional, orthogonal supramolecular pairs with high binding constants.[17] This aided our initial diblock copolymer assemblies such as helix-helix and sheet-coil. More complex systems, such as the all-covalent triblock copolymers or the heterotelechelic helix, necessitated the development of a new CTA/initiator or a different post-polymerization functionalization strategy, respectively. Characterization techniques, such as CD spectroscopy, WAXS, DOSY, and viscometry, centered upon confirming self-assembly and the retention of our secondary structures in its wake.

Some of the main challenges associated with developing bio-inspired, synthetic, supramolecular systems include structural definition/complexity and the elimination of heterogeneity. Despite great strides in the direction of perfect sequence specificity,[7] it remains a difficult challenge and perhaps unnecessary for some applications. Research from the Meijer group on substrate-bound SCNPs suggests that a cohort of polymers with some dispersity all function similarly as catalysts.[69] To address structural definition, our group used polymers with pre-defined architecture instead of performing post-polymerization cross-linking.

We have yet to explore certain aspects of our secondary structure-containing materials, such as the effect of block length on phase segregation. The Korley group's hybrid polymers containing peptides and synthetic units show structural, and thus mechanical, changes as a function of peptide content.[70] Hydrogen bonding, an important aspect of Korley's bio-based polymers, also modulates phase segregation in purely synthetic systems such as Binder's, where polymers contained MRUs of different association constants on the chain ends.[58] We predict interesting properties to result from various combinations of PIC/PMAc helices and PPV sheets, possibly with incorporation of hydrogen bonding units into the different blocks.

The photophysical properties and morphology of our PPV sheets justify more attention. Temperature and solvent dependent emission studies, as well as film fluorescence measurements, often explain the aggregation behavior of PPV strands.[66, 67, 71] Recent work from the Birkedal group examined changes in DNA-functionalized PPV aggregation and optical properties.[72] With respect to peptidic β-sheets, the van Hest group showed that unwanted aggregation can be avoided by appending PEG.[73] Hence, we expect modification of the side-chains of our sheets with PEG or MRUs, for example, to tune their photophysical and morphological properties. Furthermore, AFM could corroborate the conclusion of a compact, folded structure from our

single molecule polarization studies of the (PPV-b-PNB-b-PFP-b-)$_n$PPV sheets. This folded polymer may possess few defect sites for charge recombination, like the semiconducting polymer PTB7,[74] and could potentially serve as a p-type material in organic photovoltaics.

A recent essay highlights milestones of chemistry beyond the molecule and suggests a tool to catalog and predict well-ordered architectures called the Periodic System of Supramolecular Elements, akin to the Periodic Table.[10] Though still a work in progress, this table lists structures such as three-helix bundles, coiled-coils and β-barrels that presage a tantalizingly-higher level of complexity for our bio-inspired systems. In particular, synthesis of a three-helix bundle or coiled-coil of helical polymers requires functionalization techniques already within our reach. Nature achieves complexity by a modular and cooperative approach. With our "plug and play" strategy in place to combine secondary structure-containing polymers in diverse combinations we can now turn to incorporating functional centers into our constructs. The precise and single-handed spatial arrangement of functional side-chains on our helices in concert with appropriately tuned sheets and/or coils may encompass a mass of highly desired applications for Nature-mimicking polymers such as catalysis, chiral recognition, or artificial photosynthesis. Our strategy should enable us to assemble complex structures using well-known pieces of the puzzle.

Word Count: 4998

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Acknowledgements

The authors acknowledge financial support from the National Science Foundation under award number CHE-1902917.

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Marcus Weck obtained his Ph.D. degree in 1998 from Caltech with Robert H. Grubbs. After a two-year postdoctoral stay at Harvard University with George M. Whitesides, he joined the faculty at Georgia Tech. In 2007, he moved to NYU where he is a Professor in the Chemistry Department. His research interests are in organic and polymer chemistry as well as materials and colloid science. The main foci of his group are in supported catalysis and the introduction of complexity through the use of orthogonal functionalization methods and to synthesize polymers, organized assemblies, biomaterials, and nanostructures.

References

1. Elacqua, E.; Croom, A.; Manning, K. B.; Pomarico, S. K.; Lye, D.; Young, L.; Weck, M. Supramolecular Diblock Copolymers Featuring Well-defined Telechelic Building Blocks. *Angew. Chem., Int. Ed.* **2016,** *55*, 15873-15878.

2. Pomarico, S. K.; Lye, D. S.; Elacqua, E.; Weck, M. Synthesis of sheet-coil-helix and coil-sheet-helix triblock copolymers by combining ROMP with palladium-mediated isocyanide polymerization. *Polym. Chem.* **2018,** *9*, 5655-5659.

3. Elacqua, E.; Manning, K. B.; Lye, D. S.; Pomarico, S. K.; Morgia, F.; Weck, M. Supramolecular Multiblock Copolymers Featuring Complex Secondary Structures. *J. Am. Chem. Soc.* **2017,** *139*, 12240-12250.

4. Elacqua, E.; Geberth, G. T.; Vanden Bout, D. A.; Weck, M. Synthesis and folding behaviour of poly(p-phenylene vinylene)-based β-sheet polychromophores. *Chem. Sci.* **2019,** *10*, 2144-2152.

5. Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. Supramolecular Polymers. *Chem. Rev.* **2001,** *101*, 4071-4098.

6. Frisch, H.; Tuten, B. T.; Barner-Kowollik, C. Macromolecular Superstructures: A Future Beyond Single Chain Nanoparticles. *Isr. J. Chem.* **2020,** *60*, 86-99.

7. Nanjan, P.; Porel, M. Sequence-defined non-natural polymers: synthesis and applications. *Polym. Chem.* **2019,** *10*, 5406-5424.

8. Mattos, C.; Ringe, D. Proteins in organic solvents. *Curr. Opin. Struct. Biol.* **2001,** *11*, 761-764.

9. Gellman, S. H. Foldamers: A manifesto. *Acc. Chem. Res.* **1998,** *31*, 173-180.

10. Schmidt, H. W.; Wurthner, F. A Periodic System of Supramolecular Elements. *Angew. Chem., Int. Ed.* **2020,** *59*, 8766-8775.

11. Gimenez-Andres, M.; Copic, A.; Antonny, B. The Many Faces of Amphipathic Helices. *Biomolecules* **2018,** *8*, 45.

12. Woolfson, D. N. The Design of Coiled-Coil Structures and Assemblies. In *Advances in Protein Chemistry*, Academic Press: 2005; Vol. 70, pp 79-112.

13. Naganathan, A. N.; Doshi, U.; Munoz, V. Protein folding kinetics: Barrier effects in chemical and thermal denaturation experiments. *J. Am. Chem. Soc.* **2007,** *129*, 5673-5682.

14. Croom, A.; Manning, K. B.; Weck, M. Supramolecular Helix–Helix Block Copolymers. *Macromolecules* **2016,** *49*, 7117-7128.

15. Elacqua, E.; Croom, A.; Lye, D. S.; Weck, M. Coil-helix and sheet-helix block copolymers via macroinitiation from telechelic ROMP polymers. *J. Polym. Sci., Part A: Polym. Chem.* **2017,** *55*, 2991-2998.

16. Deng, R.; Milton, M.; Pomarico, S. K.; Weck, M. Synthesis of a heterotelechelic helical poly(methacrylamide) and its incorporation into a supramolecular triblock copolymer. *Polym. Chem.* **2019,** *10*, 5087-5093.

17. Elacqua, E.; Lye, D. S.; Weck, M. Engineering Orthogonality in Supramolecular Polymers: From Simple Scaffolds to Complex Materials. *Acc. Chem. Res.* **2014,** *47*, 2405-2416.

18. Guichard, G.; Huc, I. Synthetic foldamers. *Chem. Commun.* **2011,** *47*, 5933-5941.

19. Zhang, D.-W.; Wang, H.; Li, Z.-T. Polymeric Tubular Aromatic Amide Helices. *Macromol. Rapid Commun.* **2017,** *38*, 1700179.

20. Yashima, E. Synthesis and structure determination of helical polymers. *Polym. J.* **2010,** *42*, 3-16.

21. Yashima, E.; Ousaka, N.; Taura, D.; Shimomura, K.; Ikai, T.; Maeda, K. Supramolecular Helical Systems: Helical Assemblies of Small Molecules, Foldamers, and Polymers with Chiral Amplification and Their Functions. *Chem. Rev.* **2016,** *116*, 13752-13990.

22. Yashima, E.; Maeda, K.; Iida, H.; Furusho, Y.; Nagai, K. Helical Polymers: Synthesis, Structures, and Functions. *Chem. Rev.* **2009,** *109*, 6102-6211.

23. Green, M. M.; Reidy, M. P.; Johnson, R. D.; Darling, G.; O'Leary, D. J.; Willson, G. Macromolecular stereochemistry: the out-of-proportion influence of optically active

comonomers on the conformational characteristics of polyisocyanates. The sergeants and soldiers experiment. *J. Am. Chem. Soc.* **1989,** *111*, 6452-6454.

24. Maeda, K.; Yashima, E. Helical Polyacetylenes Induced via Noncovalent Chiral Interactions and Their Applications as Chiral Materials. *Top. Curr. Chem.* **2017,** *375*, 72.

25. Nakahira, T.; Fan, L.; Boon, C. T.; Fukada, T.; Karato, T.; Annaka, M.; Yoshikuni, M. Effects of Side-Chain Structure and Solvent on Intramolecular Hydrogen Bonding in Isotactic Poly(methacrylamide)s. *Polym. J.* **1998,** *30*, 910-914.

26. Schwartz, E.; Koepf, M.; Kitto, H. J.; Nolte, R. J. M.; Rowan, A. E. Helical poly(isocyanides): past, present and future. *Polym. Chem.* **2011,** *2*, 33-47.

27. Xue, Y.-X.; Chen, J.-L.; Jiang, Z.-Q.; Yu, Z.; Liu, N.; Yin, J.; Zhu, Y.-Y.; Wu, Z.-Q. Living polymerization of arylisocyanide initiated by the phenylethynyl palladium(ii) complex. *Polym. Chem.* **2014,** *5*, 6435-6438.

28. Schafmeister, C. E.; LaPorte, S. L.; Miercke, L. J. W.; Stroud, R. M. A designed four helix bundle protein with native-like structure. *Nat. Struct. Mol. Biol.* **1997,** *4*, 1039-1046.

29. Kajitani, T.; Okoshi, K.; Sakurai, S.-i.; Kumaki, J.; Yashima, E. Helix-Sense Controlled Polymerization of a Single Phenyl Isocyanide Enantiomer Leading to Diastereomeric Helical Polyisocyanides with Opposite Helix-Sense and Cholesteric Liquid Crystals with Opposite Twist-Sense. *J. Am. Chem. Soc.* **2006,** *128*, 708-709.

30. Cornelissen, J. J. L. M.; Fischer, M.; Sommerdijk, N. A. J. M.; Nolte, R. J. M. Helical Superstructures from Charged Poly(styrene)-Poly(isocyanodipeptide) Block Copolymers. *Science* **1998,** *280*, 1427.

31. Cornelissen, J. J. L. M.; Donners, J. J. J. M.; de Gelder, R.; Graswinckel, W. S.; Metselaar, G. A.; Rowan, A. E.; Sommerdijk, N. A. J. M.; Nolte, R. J. M. β-Helical Polymers from Isocyanopeptides. *Science* **2001,** *293*, 676-680.

32. Kros, A.; Jesse, W.; Metselaar, G. A.; Cornelissen, J. J. L. M. Synthesis and Self-Assembly of Rod–Rod Hybrid Poly(γ-benzyl L-glutamate)-block-Polyisocyanide Copolymers. *Angew. Chem., Int. Ed.* **2005,** *44*, 4349-4352.

33. Miyabe, T.; Iida, H.; Banno, M.; Yamaguchi, T.; Yashima, E. Synthesis and Visualization of a Core Cross-Linked Star Polymer Carrying Optically Active Rigid-Rod Helical Polyisocyanide Arms and Its Chiral Recognition Ability. *Macromolecules* **2011,** *44*, 8687-8692.

34. Liu, C.; Mi, Y.-X.; Wang, R.-H.; Jiang, Z.-Q.; Zhang, X.-Y.; Liu, N.; Yin, J.; Wu, Z.-Q. Facile synthesis of well-defined ABC miktoarm star terpolymers bearing poly(ε-caprolactone), polystyrene and stereoregular helical poly(phenyl isocyanide) blocks. *Polym. Chem.* **2016,** *7*, 2447-2451.

35. Reggelin, M.; Doerr, S.; Klussmann, M.; Schultz, M.; Holbach, M. Helically chiral polymers: A class of ligands for asymmetric catalysis. *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101*, 5461.

36. Miyabe, T.; Hase, Y.; Iida, H.; Maeda, K.; Yashima, E. Synthesis of functional poly(phenyl isocyanide)s with macromolecular helicity memory and their use as asymmetric organocatalysts. *Chirality* **2009,** *21*, 44-50.

37. Huurne, G. M. t.; Palmans, A. R. A.; Meijer, E. W. Supramolecular Single-Chain Polymeric Nanoparticles. *CCS Chem.* **2019,** *1*, 64-82.

38. Thanneeru, S.; Li, W.; He, J. Controllable Self-Assembly of Amphiphilic Tadpole-Shaped Polymer Single-Chain Nanoparticles Prepared through Intrachain Photo-cross-linking. *Langmuir* **2019,** *35*, 2619-2629.

39. Altintas, O.; Artar, M.; ter Huurne, G.; Voets, I. K.; Palmans, A. R. A.; Barner-Kowollik, C.; Meijer, E. W. Design and Synthesis of Triblock Copolymers for Creating Complex Secondary Structures by Orthogonal Self-Assembly. *Macromolecules* **2015,** *48*, 8921-8932.

40. Schneider, J. P.; Kelly, J. W. Templates That Induce .alpha.-Helical, .beta.-Sheet, and Loop Conformations. *Chem. Rev.* **1995,** *95*, 2169-2187.

41. Souers, A. J.; Ellman, J. A. β-Turn mimetic library synthesis: scaffolds and applications. *Tetrahedron* **2001,** *57*, 7431-7448.

42. Malke, M.; Barqawi, H.; Binder, W. H. Synthesis of an Amphiphilic β-Turn Mimetic Polymer Conjugate. *ACS Macro Lett.* **2014,** *3*, 393-397.

43. Lu, J.; ten Brummelhuis, N.; Weck, M. Intramolecular folding of triblock copolymers via quadrupole interactions between poly(styrene) and poly(pentafluorostyrene) blocks. *Chem. Commun.* **2014,** *50*, 6225-6227.

44. Romulus, J.; Weck, M. Single-Chain Polymer Self-Assembly Using Complementary Hydrogen Bonding Units. *Macromol. Rapid Commun.* **2013,** *34*, 1518-1523.

45. Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. Aromatic Amide Foldamers: Structures, Properties, and Functions. *Chem. Rev.* **2012,** *112*, 5271-5316.

46. Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. A Field Guide to Foldamers. *Chem. Rev.* **2001,** *101*, 3893-4012.

47. Loughlin, W. A.; Tyndall, J. D. A.; Glenn, M. P.; Fairlie, D. P. Beta-Strand Mimetics. *Chem. Rev.* **2004,** *104*, 6085-6118.

48. Saraogi, I.; Hamilton, A. D. Recent advances in the development of aryl-based foldamers. *Chem. Soc. Rev.* **2009,** *38*, 1726-1743.

49. Sebaoun, L.; Maurizot, V.; Granier, T.; Kauffmann, B.; Huc, I. Aromatic Oligoamide β-Sheet Foldamers. *J. Am. Chem. Soc.* **2014,** *136*, 2168-2174.

50. Lamouroux, A.; Sebaoun, L.; Wicher, B.; Kauffmann, B.; Ferrand, Y.; Maurizot, V.; Huc, I. Controlling Dipole Orientation through Curvature: Aromatic Foldamer Bent β-Sheets and Helix–Sheet–Helix Architectures. *J. Am. Chem. Soc.* **2017,** *139*, 14668-14675.

51. Conticello, V. P.; Gin, D. L.; Grubbs, R. H. Ring-opening metathesis polymerization of substituted bicyclo[2.2.2]octadienes: a new precursor route to poly(1,4-phenylenevinylene). *J. Am. Chem. Soc.* **1992,** *114*, 9708-9710.

52. Dewhirst, K. C.; Cram, D. J. Macro Rings. XVII. An Extreme Example of Steric Inhibition of Resonance in a Classically-conjugated Hydrocarbon1. *J. Am. Chem. Soc.* **1958,** *80*, 3115-3125.

53. de Meijere, A.; Kozhushkov, S. I.; Rauch, K.; Schill, H.; Verevkin, S. P.; Kümmerlin, M.; Beckhaus, H.-D.; Rüchardt, C.; Yufit, D. S. Heats of Formation of [2.2]Paracyclophane-1-ene and [2.2]Paracyclophane-1,9-diene − An Experimental Study. *J. Am. Chem. Soc.* **2003,** *125*, 15110-15113.

54. Yu, C.-Y.; Turner, M. L. Soluble Poly(p-phenylenevinylene)s through Ring-Opening Metathesis Polymerization. *Angew. Chem., Int. Ed.* **2006,** *45*, 7797-7800.

55. Yu, C.-Y.; Helliwell, M.; Raftery, J.; Turner, M. L. Synthesis and Ring-Opening Metathesis of Tetraalkoxy-Substituted [2.2]Paracyclophane-1,9-dienes. *Chem. Eur. J.* **2011,** *17*, 6991-6997.

56. Elacqua, E.; Weck, M. Fabrication of Supramolecular Semiconductor Block Copolymers by Ring-Opening Metathesis Polymerization. *Chem. Eur. J.* **2015,** *21*, 7151-7158.

57. Yang, S. K.; Ambade, A. V.; Weck, M. Supramolecular ABC Triblock Copolymers via One-Pot, Orthogonal Self-Assembly. *J. Am. Chem. Soc.* **2010,** *132*, 1637-1645.

58. Binder, W. H.; Bernstorff, S.; Kluger, C.; Petraru, L.; Kunz, M. J. Tunable Materials from Hydrogen-Bonded Pseudo Block Copolymers. *Adv. Mater.* **2005,** *17*, 2824-2828.

59. Reuther, J. F.; Siriwardane, D. A.; Kulikov, O. V.; Batchelor, B. L.; Campos, R.; Novak, B. M. Facile Synthesis of Rod–Coil Block Copolymers with Chiral, Helical Polycarbodiimide Segments via Postpolymerization CuAAC "Click" Coupling of Functional End Groups. *Macromolecules* **2015,** *48*, 3207-3216.

60. Romulus, J.; Henssler, J. T.; Weck, M. Postpolymerization Modification of Block Copolymers. *Macromolecules* **2014,** *47*, 5437-5449.

61. Lye, D. S.; Xia, Y.; Wong, M. Z.; Wang, Y. F.; Nieh, M. P.; Weck, M. ABC Supramolecular Triblock Copolymer by ROMP and ATRP. *Macromolecules* **2017,** *50*, 4244-4255.

62. Gavrilov, M.; Jia, Z. F.; Percec, V.; Monteiro, M. J. Quantitative end-group functionalization of PNIPAM from aqueous SET-LRP via in situ reduction of Cu(II) with NaBH4. *Polym. Chem.* **2016,** *7*, 4802-4809.

63. Xu, J.; Tao, L.; Boyer, C.; Lowe, A. B.; Davis, T. P. Combining Thio−Bromo "Click" Chemistry and RAFT Polymerization: A Powerful Tool for Preparing Functionalized Multiblock and Hyperbranched Polymers. *Macromolecules* **2010,** *43*, 20-24.

64. Chen, S.; Schulz, M.; Lechner, B.-D.; Appiah, C.; Binder, W. H. One-pot synthesis and self-assembly of supramolecular dendritic polymers. *Polym. Chem.* **2015,** *6*, 7988-7994.

65. Köhler, A.; Hoffmann, S. T.; Bässler, H. An Order–Disorder Transition in the Conjugated Polymer MEH-PPV. *J. Am. Chem. Soc.* **2012,** *134*, 11594-11601.

66. Sherwood, G. A.; Cheng, R.; Smith, T. M.; Werner, J. H.; Shreve, A. P.; Peteanu, L. A.; Wildeman, J. Aggregation Effects on the Emission Spectra and Dynamics of Model Oligomers of MEH-PPV. *J. Phys. Chem. C* **2009,** *113*, 18851-18862.

67. Resmi, R.; Amrutha, S. R.; Jayakannan, M. Control of molecular aggregation in symmetrically substituted π-conjugated bulky poly(p-phenylenevinylene)s and their copolymers. *J. Polym. Sci., Part A: Polym. Chem.* **2009,** *47*, 2631-2646.

68. Zhu, X.; Traub, M. C.; Vanden Bout, D. A.; Plunkett, K. N. Well-Defined Alternating Copolymers of Oligo(phenylenevinylene)s and Flexible Chains. *Macromolecules* **2012,** *45*, 5051-5057.

69. Liu, Y.; Turunen, P.; de Waal, B. F. M.; Blank, K. G.; Rowan, A. E.; Palmans, A. R. A.; Meijer, E. W. Catalytic single-chain polymeric nanoparticles at work: from ensemble towards single-particle kinetics. *Mol. Syst. Des. Eng.* **2018,** *3*, 609-618.

70. Matolyak, L. E.; Keum, J. K.; Van de Voorde, K. M.; Korley, L. T. J. Synthetic approach to tailored physical associations in peptide-polyurea/polyurethane hybrids. *Org. Biomol. Chem.* **2017,** *15*, 7607-7617.

71. Huang, Y. F.; Shiu, Y. J.; Hsu, J. H.; Lin, S. H.; Su, A. C.; Peng, K. Y.; Chen, S. A.; Fann, W. S. Aggregate versus Excimer Emissions from Poly(2,5-di-n-octyloxy-1,4-phenylenevinylene). *J. Phys. Chem. C* **2007,** *111*, 5533-5540.

72. Gudnason, D.; Madsen, M.; Krissanaprasit, A.; Gothelf, K. V.; Birkedal, V. Controlled aggregation of DNA functionalized poly(phenylene-vinylene). *Chem. Commun.* **2018,** *54*, 5534-5537.

73. Smeenk, J. M.; Otten, M. B. J.; Thies, J.; Tirrell, D. A.; Stunnenberg, H. G.; van Hest, J. C. M. Controlled assembly of macromolecular beta-sheet fibrils. *Angew. Chem., Int. Ed.* **2005,** *44*, 1968-1971.

74. Fauvell, T. J.; Zheng, T.; Jackson, N. E.; Ratner, M. A.; Yu, L.; Chen, L. X. Photophysical and Morphological Implications of Single-Strand Conjugated Polymer Folding in Solution. *Chem. Mater.* **2016,** *28*, 2814-2822.

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