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Supramolecular Polymers – we've Come Full Circle

Takuzo Aida[a, b] and E.W. Meijer[c, d]

Abstract: Since the first polymers were discovered, scientists have debated their structures. Before Hermann Staudinger published the brilliant concept of macromolecules, polymer properties were generally believed to be based on the colloidal aggregation of small particles or molecules. From 1920 onwards, polymers and macromolecules are synonymous with each other; i. e. materials made by many covalent bonds connecting monomers in 2 or 3 dimensions. Although supramolecular interactions between macromolecular chains are evidently important, e. g. in nylons, it was unheard of to proposing polymeric materials based on the interaction of small molecules. Breakthroughs in supramolecular chemistry, however, showed that polymer materials can be made by small molecules using strong directional secondary interactions; the field of supramolecular polymers emerged. In a way, we have come full circle. In this essay we give a personal story about the birth of supramolecular polymers, with special emphasis on their structures, way of formation, and the dynamic nature of their bonding. The adaptivity of supramolecular polymers has become a major asset for novel applications, e. g. in the direction for the sustainable use of polymers, but also in biomedicine and electronics as well as self-healing materials. The lessons learned in the past years include aspects that forecast a bright future for the use of supramolecular interactions in polymer materials in general and for supramolecular polymers in particular. In order to give full tribute to Staudinger in the year celebrating 100 years of macromolecules, we will show that many of the concepts of macromolecular polymers apply to supramolecular polymers, with only one important difference with fascinating consequences: the dynamic nature of the bonds that form polymer chains.

Keywords: self-assembly · supramolecular polymers · history of polymer science · stereochemistry · soft materials

1. Introduction

1.1 From Polymers to Macromolecules

A world without polymers means a world without life. In prebiotic processes, the polymerization of many different building blocks to produce tough, hard, soft or adaptive polymers is an essential element in the origin of life on earth. Natural polymers are everywhere, even long before humans populated our planet. Once there, humans used these natural polymeric materials for every possible application they could think of without having any idea about their molecular structures. It was not until the early nineteenth century that some insights were developed. In 1832, Jöns Jakob Berzelius (1779–1848) introduced the terms polymers and isomers in his analysis of organic matter.[1] At that time, it was thought that these polymer substances consisted of ill-defined colloidal aggregates of small particles or molecules. It was not until 1920 that Hermann Staudinger (1881–1963) coined the term macromolecules – originally "Hochmolekulare Verbindungen" – in his famous article in the Berichte der Deutschen Chemischen Gesellschaft.[2] Many scientists abhorred the idea of very long molecules and it took time before the macromolecular concept was generally accepted. After this transition state, the concept of macromolecules dominated the field of polymer science and materials. As a result, polymers and macromolecules have become synonymous with each other, as Wikipedia teaches us: "A polymer (Greek poly-, "many"+-mer, "part") is a large molecule, or macromolecule, composed of many repeated subunits".[3] Indeed many of the materials properties of polymers are due to the entanglements of these covalently linked monomers in a long macromolecule or due to covalent crosslinks in a polymer network. In the twentieth century, polymer science and engineering flourished as one of the main areas in materials science and one discovery was made after the other. Seminal contributions of Carothers, Flory, Ziegler, Natta, Mark, Szwarc, Shirakawa, Grubbs and many others gave endless possibilities in generating a broad spectrum of novel macromolecules. These polymer materials were optimized in their structure and property, by which many more functions became assessable. As a result, our world became addicted to polymer materials with its unlimited range

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of applications. Today, it is impossible to imagine our life style without these polymer materials in medical devices, transportation, membranes, electronics, households, coatings, batteries, personal care, packaging and many more.

As every happy story can have its flipside, it also recently happened to polymers. Unfortunately polymer materials are now negatively confronted with their high kinetic and thermodynamic stability; being one of the key properties of these materials in many applications. Today, this high stability gives rise to an increasing sustainability issue, where these polymers are too often ending up as plastic waste in nature. New avenues should be and are under development to concur this serious challenge. The most logical approach is to facilitate recycling by introducing new concepts. One of them is to tune the ratio of covalent and non-covalent bonds in controlling the dynamics of bonds that form polymer materials.[4] By doing so, polymer processability and materials properties as well as polymer recycling can be tuned at will, provided non-covalent bonds with the right dynamics are generated, incorporated, used and reused. This possible option is a result of the successful merger of supramolecular chemistry with polymer science and engineering. It is not our intension to cover the full picture on how dynamic bonds in polymer science can be exploited successfully. For the use of dynamic covalent chemistry and vitrimers, the reader is referred to some excellent papers.[5,6] Due to our own interest, the focus of this article will be on supramolecular polymers (Figure 1). In this new class of polymers, the ratio non-covalent – covalent bonds reaches its maximum as these polymers are made by directional interactions of small molecules, yielding long polymer chains with tunable dynamics.[7] An approach that was thought to be impossible as the macromolecular nature of polymers was thought to be essential to arrive at materials properties. Before discussing the main topic of this essay, we will give a few general aspects of the use of supramolecular interactions in macromolecular polymer science.

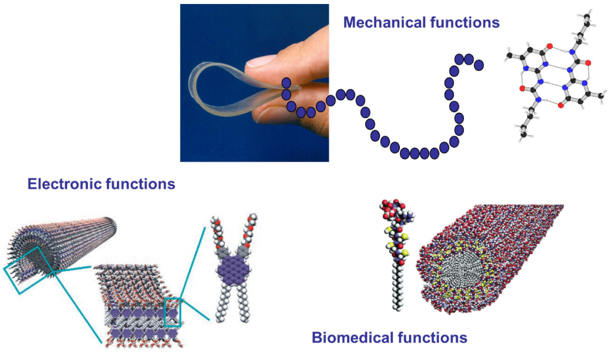

Figure 1. some examples of supramolecular polymers – adapted from Science.[7]

1.2 Supramolecular Polymer Chemistry

Before the concept of supramolecular polymers emerged, the use of specific intermolecular chain-to-chain interactions in macromolecular materials was widespread. Firstly, many secondary interactions, like hydrogen bonding, are optimized during the evolution in all natural polymeric materials to arrive at their functional state. In polysaccharides and polypeptides, it is often a combination of inter- and intramolecular interactions, where the latter takes care of the folding of polymer chains into right conformations and intermolecular interactions are in control of both the mesoscopic and macroscopic properties. The difference between starch and cellulose is a beautiful example of how differences in intra- and intermolecular hydrogen bondings, due to the stereochemistry at the anomeric center, significantly alter the properties and hence the roles of both. For polypeptides similar arguments hold, while nothing can surpass the beauty of multivalent hydrogen bonding in the double helix of DNA. Secondly, with the synthesis of nylons by Carothers, the important role of hydrogen bonding in engineering plastics was introduced. This

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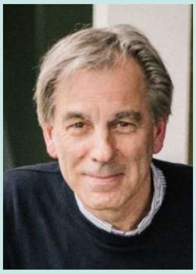

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was followed by many other important classes of polymer materials, like polyurethanes. For engineering plastics, the role of hydrogen bonding or other intra- and intermolecular interactions are used to further improve the mechanical properties at elevated temperatures. Fully aromatic polyamides provide the most stable class of polymers ever made. Because many of these secondary interactions are very stable, polymer materials usually become processable only above their melting points. For polyurethanes similar arguments hold, but some polyurethanes possess thermal reversibility of the urethane bond and can be regarded as one of the first healable materials. Later polyurethanes proved to be prime candidates for degradable biomaterials.

All of the examples above originated before the concept of supramolecular chemistry was introduced or organic chemists with their supramolecular background were involved in the research field of polymers. Although, semi-crystalline polymers can be seen as macromolecules with small aggregates due to specific non-covalent interactions. Seminal papers of Fréchet in 1989 and Stadler in 1990 are – in our view – some of the earliest examples of introducing supramolecular concepts in polymer science. Fréchet and coworkers introduced the stabilization of a mesophase through hydrogen bonding interactions in binary mixtures of polymers and small molecules.[8] A main-chain polymer was decorated supramolecularly with dangling side groups thereby generating a liquid-crystalline polymer. Stadler and coworkers used hydrogen bonds to form nano-clustered reversible crosslinks between macromolecular chains and used their dynamic nature for processing.[9] Although these examples do not represent supramolecular polymers (*vide infra*), they represent some important nuclei to the field of supramolecular polymers and certainly have brought supramolecular chemistry and polymers closer together.

1.3 The Pre-amble of Supramolecular Polymers

The pre-Staudinger idea of polymers made by molecular association never really disappeared, although no claims were made to arrive at useful material properties. In a Chemical Review of 1929, Longinescu wrote “More than fifty years ago, Louis Henry first proposed the hypothesis of molecular polymerization, now called molecular association (Annales de la Société scientifique de Bruxelles 1878, 3, 267)”.[10] Also some of the properties of imidazole in organic solvents are explained by the formation of its one-dimensional aggregate, while short stacks of chloroform molecules in chloroform are proposed recently.[11] Historically, the J- and H-aggregates of many dye molecules can be regarded as the first examples of these one-dimensional aggregates in solution, but typically they precipitate and are called pigments. After the introduction of the concept of supramolecular chemistry, chemists tried to design and study larger aggregates from small molecules, while some older studies were revisited.

The recent developments for one-dimensional aggregates or supramolecular polymers started in 1988, when one of us published the concept of cofacial assembly of amphiphilic porphyrins into one-dimensional architectures (Figure 2).[12] At that time, this discovery was not connected to any form of supramolecular polymers but was rather discussed within the field of amphiphiles by analogy to the formation of cylindrical micelles. Cylindrical micelles were considered too labile to generate materials, and this perception did not change even when much more stable polymersomes were introduced in 1995.[13,14] For these colloidal approaches and micellar aggregates the reader is referred to a comprehensive review.[15]

Independently and in the same year 1988, one-dimensional aggregates based on hydrogen bonds in the crystalline state were introduced by Wuest and coworkers.[16] They used an array of double hydrogen-bonded monomers that formed polymeric arrays in the crystal, provided that the units were designed for linear arrays, otherwise cyclic structures were obtained (Figure 3). This work was in 1990 followed by the

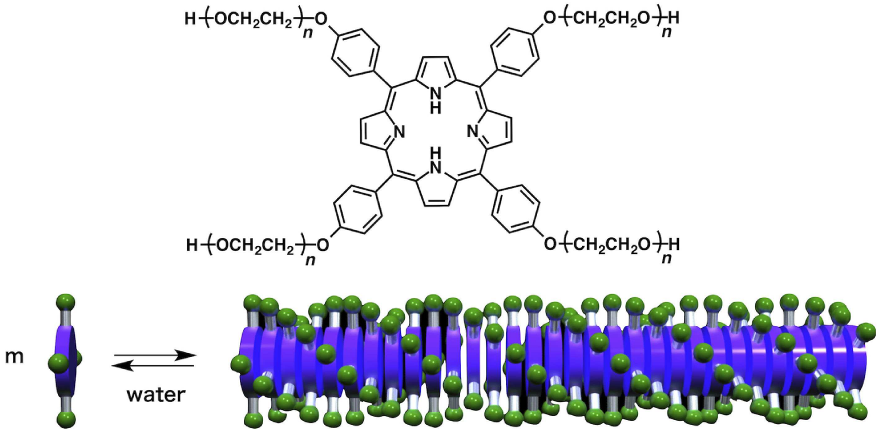

Figure 2. Cofacial 1D assembly (supramolecular polymer) of amphiphilic porphyrins.[12]

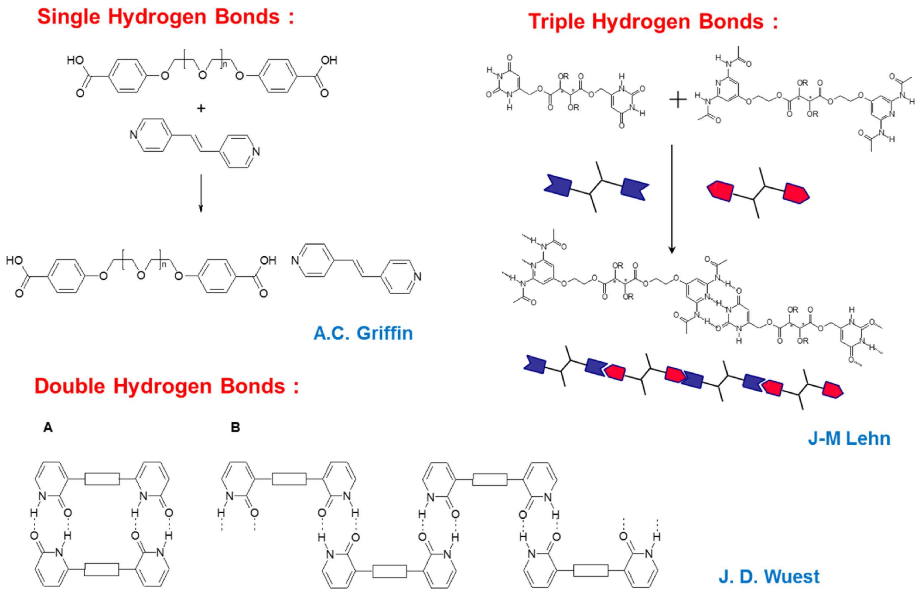

Figure 3. Some of the early hydrogen-bonded one-dimensional structures.[16,18,21]

hydrogen-bonded molecular tapes of Whitesides using melamine–cyanuric acid derivatives.[17] These examples can be regarded as supramolecular polymers in the crystalline state and in that way are similar to e.g. the crystals of terephthalic acid. Organic crystals are typically too brittle and hence do not possess materials properties. However, these examples beautifully showed a design criteria to form a polymeric array by multiple hydrogen bonds. In a next step, Lehn moved to the liquid crystalline phase using a triple-hydrogen bonded strategy in 1990.[18] Here, his group synthesized two complementary monomeric units (A-A and B-B), assembled them into a $(A\text{-}A:B\text{-}B)_n$ polymeric structure, and observed chiral fiber-like architectures with electron microscopy.[19] The rather low association constant of the triple-hydrogen bonded units was overcome by the directionality of their linear arrangement in the liquid-crystalline phase. With these seminal contributions, Jean-Marie Lehn merged the fields of polymers and supramolecular chemistry, while his polymers have often been referred to as the first supramolecular polymers.[20] In 1994, Lee and Griffin moved to amorphous materials using a single hydrogen bond between a carboxylic acid and a pyridine again in A-A and B-B arrangements.[21] In this case, the supramolecular complexes could be drawn into fibers displaying some mechanical properties, probably due to the ionic character of the bond between an acid and pyridine. Crystallization of the compounds was inhibited by substitution of the main chain with bulky chlorine atoms. Finally, Percec presented tubular supramolecular architectures as other exciting supramolecular polymers in 1994.[22] These examples (Figure 3) all make use of hydrogen bonds to bring monomers together in one-dimensional (1D) arrangement. Indeed, hydrogen bonds are ideal for achieving the directionality of the covalent bond as ionic interactions will extend their interactions to the third dimension. These examples also show that for a polymer to be formed, an even number of hydrogen bonds creates self-complementarity and only one type of monomer unit is required. An odd number of hydrogen bonds needs two different complementary monomeric units for obtaining a polymer, while controlling the exact stoichiometry is another factor to take into account.

Despite their beauty in representing the birth of supramolecular polymers, the association constants between the repeating building blocks are actually too low to furnish high virtual molecular weights of the polymers in solution, melt and amorphous states. Hence, the idea to make mechanically strong polymeric materials by 1D association of small molecules remained within the realm of fantasy. With hydrogen bonds as the ideal interaction for making supramolecular polymers, however, their strengths should be increased considerably compared to the early-stage examples with K_{ass} not exceeding $10^3\ M^{-1}$. In order to do so, the number of cooperative hydrogen bonds in an array has to be increased as well as the directionality of the dipoles along the array, as beautifully pointed out by Jorgensen.[23,24] A donor-donor-donor array that is complementary to an acceptor-acceptor-acceptor array is orders of magnitude stronger than the donor-acceptor-donor array that couples with an acceptor-donor-acceptor array. However, until the end of the previous century, no 1D supramolecular architectures structures with decent length and sufficiently strong interactions had been published that could serve as an alternative to covalent, macromolecular polymers.

2. Supramolecular Polymers as Materials

2.1 The First Mechanically Robust Supramolecular Polymeric Materials

That all changed in 1997 when the ureidopyrimidinone (UPy) self-complementary quadruple hydrogen bonding unit was introduced to this field. In close collaboration with Sijbesma, one of us developed the ureidopyrimidinone (UPy) motif and investigated its mode of action in detail.[25] The first experiments to arrive at supramolecular polymers started in 1992 and it took 5 years before the UPy motif was fully characterized and its usefulness tested. The molecule is very easy to synthesize in one step from commercially available precursor molecules or in three steps from methyl acetate. At that time, it represented the first example of a (self-complementary) quadruple hydrogen bonding unit. The analysis of the binding strength was much more difficult than the synthesis of UPy, as it is so high. A combination of techniques, including magnetization-transfer NMR studies, yielded a dimerization constant of $K_{dim} = 10^7$–10^8 M^{-1} and a life time of 0.1–1.0 second, both properties depending on the dielectric constant of the solvent. This UPy-group when attached to both sides of a spacer furnished thermodynamically stable supramolecular polymers with macroscopic properties that were traditionally only reserved for covalent macromolecules (Figure 4). Films and fibers could be prepared and these materials possess in many ways the bulk properties of macromolecular materials. Plots of modulus and complex viscosity hardly distinguish the UPy-based supramolecular polymers from their macromolecular counterparts. The high viscosities of semi-dilute solutions of the UPy-based polymers provided the first strong argument for the presence of long chains that can entangle in solution. Moreover, the steep drop in viscosity by adding a small amount of mono-UPy substituted molecules was in full line with a step-growth polymer in the presence of chain-cappers. From these data, a virtual molecular weight of half-a-million was estimated for the UPy-based supramolecular polymer in semi-dilute solution. Obviously, the purity of the bifunctional monomer must be very high for obtaining this ultrahigh virtual molecular weight. However, the addition of a small amount of trifunctional monomers can push the virtual molecular weight up to incredible numbers where the dynamic 3D network can be regarded as an entangled 1D supramolecular polymer as the dynamic crosslink resembles in many ways the dynamic reptation of a polymer chain.

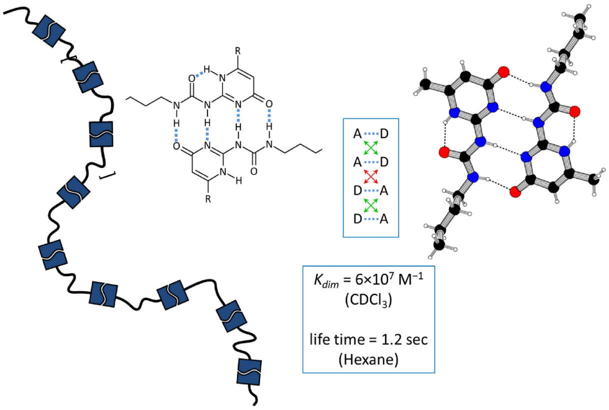

Figure 4. UPy-based supramolecular polymers as strong polymeric materials.[25]

The dynamic nature of the connection between the repeating units provide new options for processing; e. g. at higher temperatures its lifetime becomes much shorter, and the viscosity is significantly reduced. Significantly higher energies of activation (Eŋ) are found for the viscosity of supramolecular polymers than for macromolecules. The UPy-based polymers possess an Eŋ of 105 kJ/mol, while those of traditional macromolecules are in a range of 25–80 kJ/mol. Through the years the use of the UPy-motif expanded and a large number of different spacers, oligomers and even macromolecules were decorated with the UPy-motif.[26] 1D supramolecular polymers and 3D polymer networks are obtained with the UPy-unit at the end of the chain. Strong supramolecular aggregation is obtained when the UPy-unit is incorporated in the main chain and versatile thermoplastic elastomers are obtained.[27] Similar ideas were used to make highly elastic supramolecular hydrogels.[28] The incorporation of an UPy-unit to both ends of an oligomer containing also allowed for creating ordered 1D-supramolecular polymers through UPy–UPy stacking and urea–urea interactions.[29] As a result the UPy became one of the central motifs in the field of supramolecular polymer materials.[30,31] Provided appropriately designed, these materials are successfully used as adhesives for low-temperature processing or as mechanically robust elastic hydrogels, that are yet easy to recycle. The successful combination of interactions yielded supramolecular thermoplastic elastomers that are used as temporary biomaterials for regenerative medicine (*vide infra*).[32] Clinical trials for endogenous tissue restoration (ETR) are underway; a new therapeutic approach, enabling the patient's own body to naturally restore a new blood vessel. Next to new options for processing, also unique self-healing properties of supramolecular materials were discovered that created novel applications.[33,34] Finally, the modular approach, where different structures all modified with the same supramolecular motif, created unlimited modifications of the supramolecular polymers by just mixing. These UPy-based polymers were in a way the start of the field of supramolecular polymers as materials with the following definition: *Supramolecular polymers are defined as polymeric arrays of monomeric units that are brought together by reversible and highly directional secondary interactions, resulting in polymeric properties in dilute and concentrated solutions, as well as in the bulk. The monomeric units of the supramolecular polymers themselves do not possess a repetition of chemical fragments. The directionality and strength of the supramolecular bonding are important features of systems that can be regarded as polymers and that behave according to well-established theories of polymer physics.*[31]

2.2 The New Field of Supramolecular Polymers

Indeed, it was from 1997 onwards that the field of supramolecular polymers as materials witnessed an unexpected expansion following the early examples described above. Seminal contributions were made by Zimmerman, Leibler, Craig, Bouteiller, Zhang, Binder and Long, just to name a few.[33,34,35,36,37,38,39] Next to hydrogen bonds, coordination bonds were introduced into the field of supramolecular polymers, as well as supramolecular polymers based on host-guest chemistry.[37,40,41] Both are highly interesting, show great progress and have great potential, but are not discussed here and the reader is referred to a comprehensive review.[37] Through the years, the research field of supramolecular polymers and their materials has grown to a new discipline in polymer science especially since novel functionalities were incorporated into these supramolecular polymers. It is now well respected that the use of non-covalent bonds in polymer materials give much more options than expected before. Especially the dynamic nature of the non-covalent bonds makes these polymer materials adaptive, healable, reformable and easy to process and recycle. An illustrative example for one of these features is the introduction of self-healing polymer glasses. The proper design using thiourea functionalities and their dynamic hydrogen bonding gave rise to mechanical robust yet healable properties at ambient temperatures.[42] This achievement updated the preconception in polymer science that mechanical robustness and healing properties are mutually exclusive.

The field of supramolecular polymers started with the idea to make new materials in bulk. However, the notion that self-assembly of small molecules in solution creates structures resembling – to a great extent – macromolecules in solution resulted in many fundamental studies. Most notably are the highly-ordered supramolecular polymers in (semi-)dilute solution, mimicking the natural fibers and filaments. In retrospect, the amphiphilic porphyrins introduced by one of us, can be regarded as the first supramolecular polymer in solution (*vide supra*). The studies in solution are often not directly targeting a specific application, but are aiming at broadening the scope and limitations of supramolecular polymers as well as introducing new concepts. Almost simultaneously with the first UPy-based polymers, Rebek published the strong association between urea substituted calix(4)arenes to design 'polycaps' (polymeric capsules) formed from monomers that contain two covalently linked calix(4)arene tetra-ureas.[43,44] In chloroform, the polymers are formed reversibly, as was shown by depolymerization upon the addition of mono-functional chain-cappers. The breakthrough came when discotic liquid crystals were assembled in dilute apolar solvents using multiple interactions.[12,45,46] The assembly process was based on solvophobic effects and resulted in micrometer-long one-dimensional supramolecular polymers. Some of the most studied supramolecular polymers of this category are presented in Figure 5.

One of us reported in 2004 the first molecule capable of nano-tubularly polymerizing in solution. This molecule features a hexabenzocoronene core having two triethyleneglycol chains on one side and two dodecyl side chains in the other (Figure 5).[47,48,49,50] The tubes obtained were electroconductive and used as novel electronic materials in devices (*vide infra*). Another special class of one-dimensional supramolecular polymers is the one that is self-assembled in water, e.g. peptide-amphiphiles from the laboratory of Stupp. These biological relevant supramolecular polymers have been studied in detail for their applications in tissue engineering and

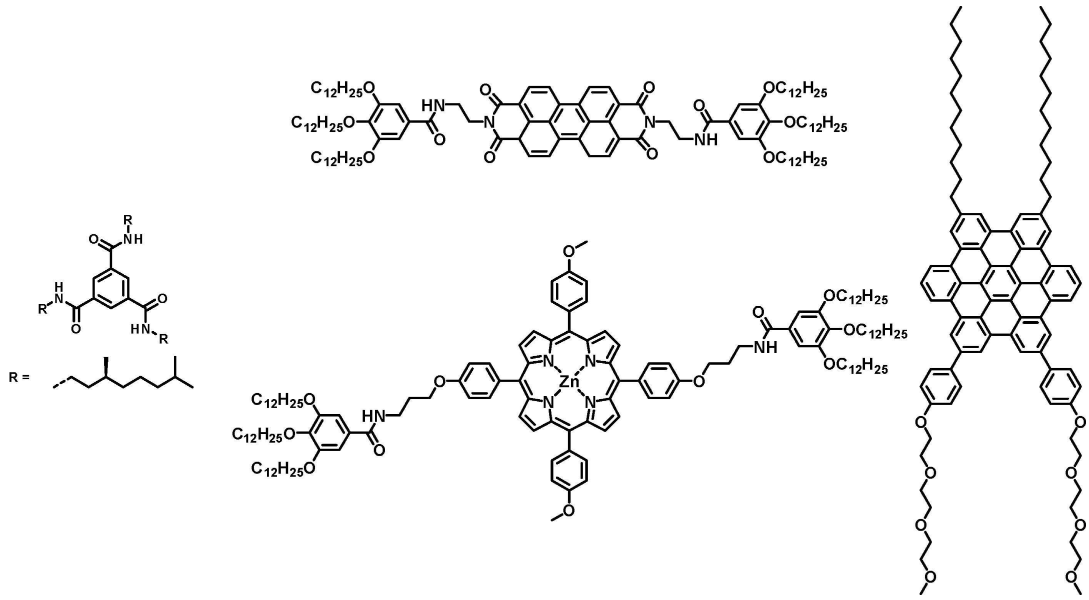

Figure 5. Some of the most studied ordered supramolecular polymers.[12,45,47,48]

regenerative medicine.[51,52] They are studied both as isolated fibers and as part of hydrogels when the concentration of the peptide amphiphiles is increased; here weak chain-chain interactions yielded bundling and hence hydrogels. Many more supramolecular polymers in water are disclosed to form dynamic supramolecular hydrogels. The field became very active for the design of biomaterials as artificial extracellular matrices, their use in cell-biology and in the clinic. For details of the different polymers disclosed, the reader is referred to two of the many reviews written on this topic.[53,54] Here, we like to focus on a few specific topics; topics of our personal interest that certainly do not cover the whole spectrum of supramolecular polymers, but gives us excitement and many new insights into the dynamic behavior of supramolecular polymers.

3. Mechanisms of Supramolecular Polymers

Already in his seminal review on polymerization in 1931, Wallace H. Carothers divided polymers according to the mechanisms of their formation – a model that is still operative in most undergraduate classes in polymer chemistry today.[55] Most remarkably, he recognized this subdivision just eleven years after the concept of macromolecules was coined by Staudinger and a few years after that idea was generally accepted. The three mechanisms operative in macromolecular polymerizations are; 1) condensation (now step) polymerization; 2) addition (now chain) polymerization; and 3) polymerization involving cyclic compounds (now ring-opening polymerization). It is instrumental to understand the structure and properties of polymers by its mechanism of formation and is used to educate students in their first polymer classes, indeed. Today it is also well accepted that the same subdivision is operative for supramolecular polymerizations.[56] Obviously, the concept is adjusted to the dynamics of the bonds formed, by which thermodynamics often overrules kinetic control. Before going into some of the details, it is important to define the molecular weight of a supramolecular polymer. With supramolecular polymers it makes more sense to use the term "virtual molecular weight" as measured with techniques having a timescale faster than the lifetime of the interacting bonds. This means that the virtual molecular weight is formally dependent on the techniques used. However, with the same technique and the same building blocks, it is appropriate to compare molecular weights as a function of temperature, concentration or the presence of additives if any added, like chain-cappers. It is also difficult to discuss the issue of forming cyclic supramolecular polymers when their virtual molecular weights are high. At every point in time, when one linkage in a large cycle is broken, the difference between large cycles and linear chains becomes semantic.

Following Carothers' approach, we recognize two main mechanisms of formation in supramolecular polymerizations: either the stepwise (also isodesmic) polymerization or the nucleation-elongation (also cooperative) polymerization (Figure 6).[7] An isodesmic or equal K-model is operative for the formation of all random-coil supramolecular polymers or any other polymer in which the association constant of the bonding is independent of the polymer length. Isodesmic polymerization is in almost all aspects similar to step polymerization for the formation of macromolecules. Hence, the virtual molecular weight can be controlled by using mono-functional units that will act as chain-cappers. When isodesmic polymerization is carried out with complementary binding units, their equal molarity as well their high purity and high association constant is critically important, again similar to polycondensation. The stoichiometry issue is not present when self-complementary units are used or monomers with both complementary units connected by one spacer. The UPy-based polymers, discussed above, follow in many ways the isodesmic polymerization and – if you like – can be compared to vitrimers at high temperatures. The virtual molecular weight at semi-dilute concentrations is estimated to be roughly 0.5×10^6 Dalton and can be tuned by adding mono-functional chain-cappers. It turned out to be very difficult to measure the "virtual" molar mass distribution, but they all should follow Flory's statistics with $Đ=2$. As far as we know, all isodesmic polymerizations reported so far are under thermodynamic control.

When monomers supramolecularly polymerize to shape-persistent and highly ordered one-dimensional filaments, the process resembles a one-dimensional crystallization and hence a nucleus is required to start the polymerization. The so-called cooperative or nucleation-elongation mechanism, thus described, is operative in many cases studied so far. It provides multiple opportunities to control the structure at mesoscopic length scales, like the hexabenzocoronene-based tubes or peptide-amphiphile fibers (*vide supra*). The cooperative mechanism for supramolecular polymerization to form 1D polymers was first analyzed in detail for discotic dyes.[56] Detailed studies under thermodynamic control for temperature-induced polymerization revealed the requirement of nucleus formation before elongation to longer polymers can set in. Nuclei composed of 3–6 or even 25–35 molecules were reported, depending on the type of monomer used. The monomer concentration determines the temperature (by slow cooling) at which elongation starts. Models introduced by Goldstein and Stryer for protein assembly were used to

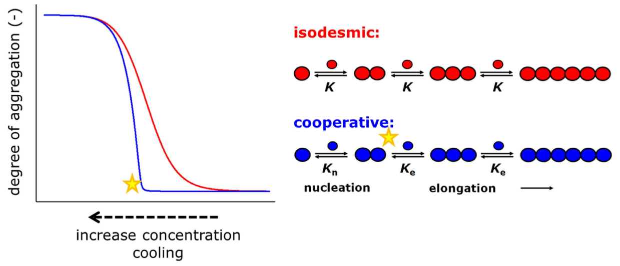

Figure 6. The two possible mechanisms of supramolecular polymerization.

determine the equilibrium constants K_{nucl} and K_{el} for the nucleation and elongations, respectively.[57] The cooperativity factor σ is related to the nucleation penalty (NP) by $\sigma = \exp(NP/RT)$ and forms a continuous spectrum from 1 (isodesmic) to $>10^{-6}$ (highly cooperative), depending on the type of monomer. During the process of a highly cooperative polymerization, only long polymer chains are present next to monomers, similar to chain polymerization to from covalent macromolecules. In the meantime, a variety of detailed studies on novel cooperative supramolecular polymerizations have been reported and the general concepts are well-accepted. In many cases, it resembles 1D crystallization of organic molecules, and thus polymorphism can be expected. Indeed in 2015, it became clear that pathway complexity is a serious issue in these cooperative polymerizations.[58] Often the monomer first aggregates into a kinetically-preferred structure, then depolymerizes and subsequently polymerizes to form a thermodynamically-preferred structure (Figure 7). If the kinetic structure is relatively stable, thermal annealing is required to arrive at the thermodynamically-preferred structure. The principle of pathway complexity is usually overlooked, but is of prime importance to design pathway-selective structures and preferred aggregation processes.

A very special case following the cooperative mechanism is the seeded or nucleus-initiated "living" polymerization of small molecules. Here, the monomer is hampered for polymerization due to intramolecular interactions or because it is trapped in a kinetic-controlled aggregate.[59,60,61] The addition of nuclei of the thermodynamic state to the trapped state will initiate polymerization (Figure 8). If the nucleation is performed properly and the supramolecular polymerization is not too fast in its dynamics (*vide infra*), it is even possible to limit

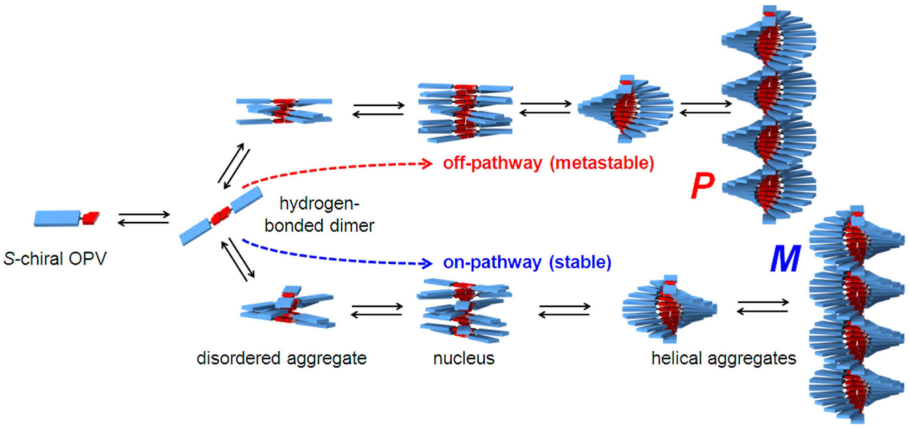

Figure 7. Pathway complexity in cooperative supramolecular polymerization – adapted from Nature.[58]

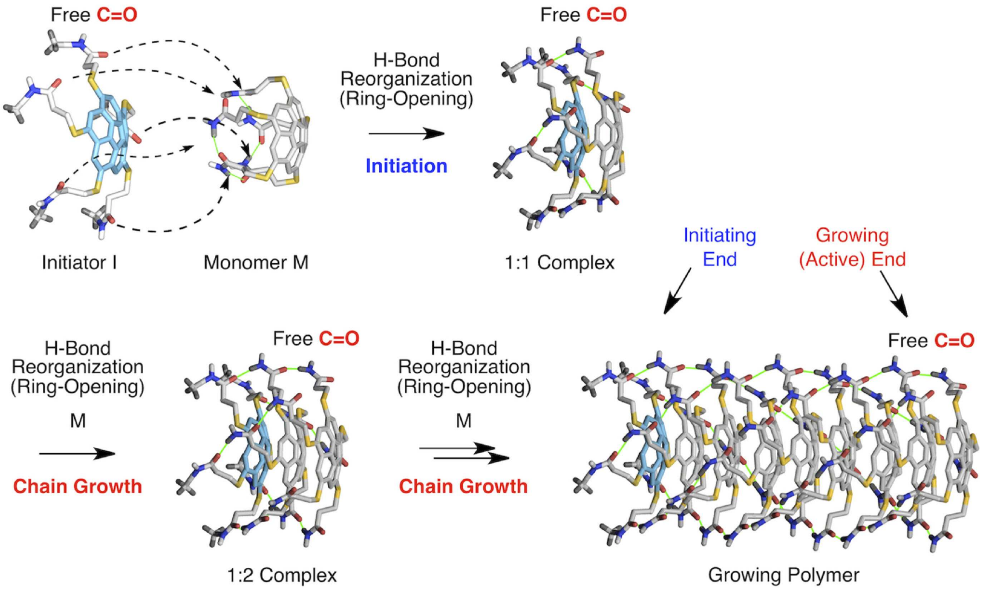

Figure 8. Chain-growth (ring-opening) supramolecular polymerization – adapted from Science.[60]

the polydispersity and to create supramolecular block copolymers. The "living" polymerization approach on the basis of this concept has been first reported by Manners and Winnik.[62] They used block copolymers as the monomeric building blocks to prepare supramolecular structures that really crystallize in what is now termed "living crystallization-driven self-assembly (CDSA)".[63] The process permits control over the length of cylindrical micelles to form block co-micelles. Many beautiful examples followed the initial paper in 2007 and Manners wrote an outstanding review recently.[64] Very recently, Würthner, being one of the pioneers in the field, wrote an excellent review on the supramolecular polymerization through kinetic pathway control and living chain growth.[65] He also suggest an interesting concept calling a supramolecular polymerization 'living' when it is demonstrated that the growth of the supramolecular polymer is only from the active ends, otherwise the polymerization should be called kinetically controlled or seeded.

Although most of the polymerizations are governed by an isodesmic or nucleation-elongation mechanisms, one of us reported in 2015 a new strategy to realize ring-opening supramolecular polymerization (Figure 8), where the monomer is designed to adopt a closed architecture by kinetically preferred "intramolecular H-bonds" and requires an initiator to polymerize, just like chain-growth polymerization in conventional polymer synthesis.[60] Consequently, polymers with controlled molecular weights and a narrow polydispersity are available. Finally, the description of supramolecular polymerizations in water requires some special attention, here hydrophobicity is often combined with, for instance, hydrogen bonding, as in the peptide amphiphiles. The studies are hampered by the fact that both effects have different dependencies on concentration and temperature. Moreover, the bundling of supramolecular polymers is difficult to control, as it takes place by secondary nucleation or by non-specific interactions. In other words, further detailed insights into the dynamic nature of supramolecular polymers is essential to the understanding of the polymer properties.

4. Dynamic Behavior of Supramolecular Polymers

As discussed above, supramolecular polymers resemble covalent macromolecules in many ways, except the dynamic nature of the interactions keeping the monomers together. Without doubt, studying the details of these complex dynamic characteristics is one of the most fascinating aspects of supramolecular polymers. However, also one of the most difficult ones to fully unravel, both for studying the polymers in semi-dilute solution and in the bulk, with each their own challenges. A comprehensive description goes beyond the scope of this article; only a few topics will be described here, as many new insights will come available in the years to come.

The thermodynamic stability of a supramolecular polymer is often described with K_{ass} (*vide supra*). When K_{ass} is too low ($K_{ass} \leq 10^4\ M^{-1}$), the aggregates are typically small in size and do not show any interesting properties. Similarly, if K_{ass} is too high ($K_{ass} \geq 10^{10}\ M^{-1}$), the resultant supramolecular polymer behaves just like covalent polymers due to the lack of dynamics. Hence, most of the interesting supramolecular polymers possess values for K_{ass} in-between the values above. However, as in biochemistry, the on-off rates (k_{on} and k_{off}) are equally important and often describe the main characteristics of supramolecular polymers. As well accepted, $K_{ass} \cong k_{on}/k_{off}$ and thus the same value of K_{ass} can be obtained with small k_{on} and k_{off} values as well as with large ones. This dynamic property is important as very large k_{on} and k_{off} will typically give labile and highly adaptive systems, while with slow rates the supramolecular polymer is more robust and easier to investigate. Contrary to macromolecules, the time resolution of the technique used to study the polymers will give different answers. Moreover, again the difference between supramolecular polymers based on the isodesmic mechanism and nucleation-elongation mechanism is striking.

The isodesmic model makes an analysis on dynamics rather simple and straightforward. Although for mechanical properties, K_{ass} is less interesting than the lifetime of the supramolecular interaction. With the lifetime known, it is possible to calculate the virtual molecular weight of the polymer, i.e. the average length of a chain of monomers held together. In the case of UPy-based polymers in semi-dilute solution with a lifetime of one second of the supramolecular bond, we come to average molecular weights of more than half-a-million are estimated. In the bulk, the lifetime can be estimated by dynamic mechanical analysis. Then the actual molecular weight will be even higher due to the full packing of space and the importance of discussing the molecular weight vanishes. This is even truer, when the Tg of the supramolecular polymer material is above the temperature of operation. As most of the applications make use of polymer materials based on the isodesmic nature, e.g. self-healing and recycling (*vide infra*), it is evident that many studies in the future will discover some exciting features.

For highly-ordered supramolecular polymers in solution based on the nucleation-elongation model, the discussion about dynamics becomes much more fascinating and more difficult at the same time. Many questions are relevant for this topic. Does a rigid rod polymer possess equal dynamics along the chain? Are there defects in the chain and when do we call it a defect and when a chain-end? What does a persistence length mean? Is the growth of the polymer only at the ends? If so, at both ends or only at one? Can the exchange happen by sliding of monomers in and out of the stack and at which place? Will they do it one-by-one or in small aggregates? What is the difference between water and organic solvents? Many more challenges can be raised that are prone to be answered.

Due to hydrophobic forces present for assemblies in aqueous solutions, the dynamics in water are really different and often more difficult to grasp than in organic solvents. Supramolecular polymerization in water often starts from small micelle-like aggregates that polymerize to long supramolecular filaments. However, simple curves like in Figure 6 are often not observed. The discrimination between isodesmic and cooperative formation of the polymers often lacks in many studies, while cryo-TEM shows micrometer long fibers or tubes. On the other hand, techniques developed for biochemical systems can be used to obtain more information about the dynamics once the polymer is formed. Hydrogen-deuterium exchange followed by mass spectrometry,[66] super-resolution microscopy,[67] and electron paramagnetic resonance combined with Overhauser dynamic nuclear polarization experiments[68] are just a few. All these techniques indicate that most – if not all – of the (highly) ordered supramolecular polymers have different domains with their own exchange rates. Next to the presence of small micelles, the polymers show parts that are almost perfectly ordered and highly persistent, but also parts that are more disordered with reasonable fast exchange rates. Coarse-grained calculations confirm the exchange via 'so-called" defects in the highly-ordered stacks.[69] Hence, while static techniques – like cryo-TEM – indicate straight and highly-ordered filaments, studying the dynamic nature in water clearly show the diversity in order of these structures. Similar phenomenon have recently been observed for natural supramolecular polymers, like collagen fibers, beta-amyloid and microtubules.[70,71] When organic solvents – like isopropanol, THF or acetonitrile – are added to the aqueous solutions of supramolecular polymers, their dynamics are increased and the monomer state is preferred. The supramolecular polymer typically falls apart if the phase-diagram of the solvent combination shows phase separation into a water-rich domain and an organic solvent-rich domain.

For highly-ordered supramolecular polymers in organic solvents ranging from chloroform to heptane, the dynamics are more straightforward, but experimentally and theoretically more difficult to study. Due to a broad range of solvents with different dielectric constants, the exchange rates in organic solvents can range significantly. Supramolecular polymers with exchange rates as fast as a fraction of seconds at room temperature are reported, but also polymers exist that have stabilities of weeks at the same temperature. Typically, exchange rates become higher at elevated temperatures, although some molecule – solvent combinations show the opposite (*vide infra*). Depending on the stability of a supramolecular polymer at the temperature of study, the exchange happens primarily at the ends and at defects for stable stacks. However, more dynamic polymers can show exchange throughout the stack. Theoretical simulations of the kinetics of dynamic supramolecular polymers fit very well with the data by just taking the exchange by polymerization and depolymerization at one end of the stack. When the exchange rates become very low, it is even possible to make block copolymers that remain stable for weeks at lower temperature as the kinetically trapped states, as beautifully shown by Würthner and coworkers.[72] Only a few examples of thermodynamically stable supramolecular block copolymers are reported.[49,60,73] It will take some time, before all the secrets of the dynamics of supramolecular polymers are fully unfolded.

Finally, the influence of additives (e.g. co-solvent or chain-capper) to change the dynamics and hence the stability of the supramolecular polymers is discussed. When a good solvent, for instance chloroform, is added to a supramolecular polymer in a poor solvent, for instance heptane, the polymer disassembles. In many cases this process is due to a larger k_{on} and k_{off} where the monomeric state is preferred by the good solvent. When the good solvent destabilizes the polymer, it often stabilizes the monomer. Detailed studies showed the resemblance with the urea-induced unfolding of proteins. As these studies are often performed in a mixture of solvents, it is also very important to understand the properties of the solvents themselves, as they determine many aspects of the system as a whole. For instance the nanoscopic phase separation of two solvents versus molecularly mixed solvents can have a distinct influence on the dynamic behaviors of supramolecular polymers. Therefore, much more research is needed to fully capture these behaviors. Two illustrating examples have been presented recently. Firstly, supramolecular polymerization of a H-bonding porphyrin polymerization in a hydrocarbon solvent containing a minute amount of a H-bond scavenging alcohol shows distinct pathways in a thermally bisignate supramolecular polymerization (Figure 9).[74,75] Secondly, minute amounts of molecularly dissolved water molecules in apolar solvents, like methylcyclohexane, become part of the supramolecular polymer at lower temperatures, due to specific H-bonding interaction between the monomer and water.[74,75]

5. Chirality and Supramolecular Polymers

With the notion that ordered supramolecular polymers formed by cooperative mechanisms often adopt a helical geometry, an interest in studying supramolecular chirality in these polymers emerged.[77] In many cases, the monomeric units are disc-shaped and lack the freedom of fast rotational motion in the supramolecular polymer due to strong intermolecular interactions, most often via hydrogen bonds. Therefore, the preferred conformation of such polymers is a helix. Maybe

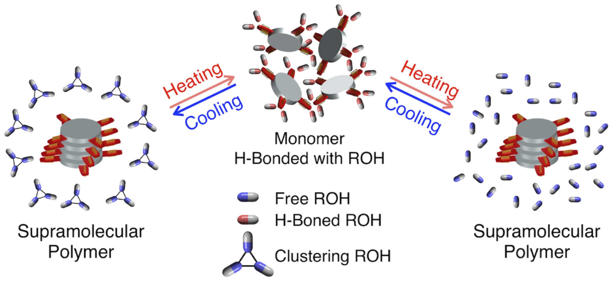

Figure 9. Distinct pathways in thermally bisignate supramolecular polymerizations.[74,75]

more correctly, of all possible conformations the one where the monomers are stacked in a helical stair-wise fashion is the lowest in energy and therefore dominates the structure. When the monomers are achiral, both P and M helices are formed in equal amounts. When the monomers are chiral, typically due to the presence of one or more stereocenters in the side chains, the diastereomeric relationship between P and M helices leads to the preference of one of both. Most remarkably, but in close resemblance to dynamic chiral covalent polymers, the cooperativity of the assembly requires only a tiny difference in energy at the monomer level to yield a significant – and often 100 % – preference of one-handed helical form at the supramolecular level. This strong preference is easy to understand by taking the cooperativity of the system into account. With a cooperative length of 200 repeating units, the free energy of 50 J/mol at the monomer level becomes 10 kJ/mol at the level of the polymer. Many of these chirality issues have been studied using benzene-1,3,5-tricarboxamides (BTAs, Figure 5). BTAs form supramolecular polymers with fast exchange dynamics that are in a thermodynamic equilibrium state. Hence, BTA-based polymers are showcases for the impact of cooperativity to bias helicity in supramolecular polymers. Detailed studies unraveled the so-called sergeant-and-soldiers and majority-rules principles, as beautifully introduced by Green for dynamic covalent helical macromolecules.[78] In other words, when chiral monomers added in a small fraction, such as 5 %, to achiral monomers, they often determine the overall helical sense of the resulting polymers. Similar effects can be obtained for mixtures of enantiomers with an unequal amount of R and S monomers (Figure 10).[79,80] In the latter, it is important that the so-called mismatch penalty of the "wrong" monomer in the opposite helicity is not too high – otherwise a conglomerate is formed. Many examples of both mixing and self-sorting are known although a rationale to predict the outcome is absent. We demonstrated that self-sorting and homochiral supramolecular polymerization allow for the separation of enantiomers.[81] Namely when the enantiomeric monomers with a bis(cyclic dipeptide) motif are present in different amounts, self-sorting gives polymers with different lengths for both helicities. Using achiral GPC, these polymers are separated and hence enantiomers are separated. In a recent review, Sanchez described many more important examples of C3-symmetrical π-scaffolds as useful building blocks to construct helical supramolecular polymers.[82] This review includes the triphenylamine-based building blocks as introduced and studied in detail by Giuseppone, which was recently reviewed as well.[83]

As described above, supramolecular chirality is used to study not only the mechanism of the formation of supramolecular polymers, but is also useful for arriving at detailed insights into the conformational preference of these polymers. Through the years, a variety of stereochemical effects have been studied using chiral supramolecular polymers. A few examples are given here; 1) chiral solvents can induce preferred helicity;[45] 2) chiral polymers can be used as catalysts for asymmetric synthesis;[84] and 3) circular polarized luminescence can be observed in chiral polymers.[85] Next, recent examples show that these chiral polymers can also be used in the so-called chiral induced spin selection (CISS effect) as pioneered by Naaman and Waldeck.[86] The stacking of dyes in polymers with preferred helicity was used to demonstrate spin-selection in the photochemical splitting of

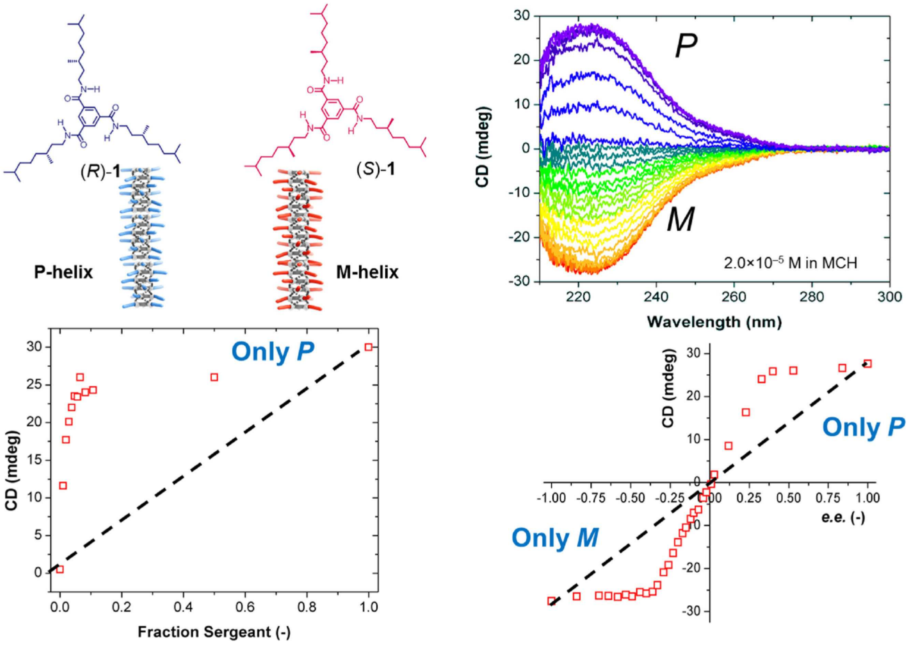

Figure 10. Sergeant-and-soldiers and majority-rules principles for BTA-based supramolecular polymers.[77,78]

water in hydrogen and oxygen.[87] This option is only at its infancy, and much more results are needed to fully explore this fascinating approach. In conclusion, the combination of chirality and polymers affords many insights for comparing macromolecular and supramolecular polymers; they show unforeseen similarities.

6. New Functions Using Supramolecular Polymers

The specific dynamic nature of supramolecular polymers gives rise to a number of highly interesting properties. Obviously, the ease of processing is one of the first highlights. The viscosities of UPy-based polymer materials are highly temperature dependent ($E_\eta = 105$ kJ/mol – using Andrade-Eyring equation), furnishing low viscosities at elevated temperatures.[84] Appropriate design of the components enables materials with strong mechanical strengths, but also low flow viscosities at relatively low temperatures. For an ideal flow for processing, covalent polymers with the same mechanical strengths typically require 100 degrees higher temperatures than their supramolecular analogues. The ease of processing also makes recycling of supramolecular polymer materials much more attractive.

Self-healing of polymeric materials is without doubt one of the most exciting new function, as introduced by Leibler and coworkers in their seminal Nature paper.[33] This example sparked many others to explore self-healing supramolecular materials using a variety of structures, while reversible covalent bonds – as in vitrimers – are introduced as well. For long, the idea to having a glassy material that can self-heal at room temperature remained a challenge. Recently, one of us introduced an innovative polymer glass, which is mechanically robust ($\varepsilon = 1.4$ GPa) but can self-heal, even at room temperature, just by compression at fractured surfaces.[42] The polymer glass is composed of a supramolecularly polymerized oligomeric ether thiourea. A key finding is that its H-bonding array is irregularly bent and, even though densely formed, barely promotes crystallization. Together with their subsequent discovery of a self-healable high-temperature porous material composed of very rare CH···N bonds, the invention of self-healable polymer glass updated the preconception that only soft rubbery materials can heal.[89] These seminal works certainly contribute to the realization of sustainable society.

Next to the use of supramolecular polymers for unique mechanical properties, this new class of polymers also is extensively studied for their used in electronic and biomedical applications. The idea of supramolecular electronics has been investigated by both of our groups.[90,91] The first electroconductive nanotubular supramolecular polymer from amphiphilic nanographenes, i.e. hexabenzocoronene, was published in 2004.[47] Nanotubular polymers are categorized into one-dimensional objects, but their wall structures adopt a two-dimensional geometry (Figure 11). Their synthetic strategy is totally different from those for ordinary 1D supramolecular polymers. By the use of this amphiphilic hexabenzocoronene platform, it was also possible to noncovalently synthesize radial and 1D supramolecular block copolymers.[48,49] Seminal contributions by Würthner and coworkers include supramolecular polymers based on perylene bisimides (PBIs).[72] Careful design of monomers and pathway selection in the polymerization yielded many different one-dimensional fibers with unique optical and electronic properties. Also fascinating exciton-migration over micrometers lengths due to excitonic order were reported in supramolecular polymers.[92] All these examples will make a next step possible where supramolecular polymers in real-world devices are coming closer to reality.

Biomedical applications of supramolecular polymers have also been studied extensively. The seminal work of Stupp created supramolecular filaments that mimic in many aspects natural filaments. The assembled peptide amphiphiles are used in tissue engineering with many fascinating results.[54] Also UPy-based polymeric materials are effectively used to regenerate vascular grafts in humans, and many clinic trial are in progress. Finally, by using the concept of supramolecular polymerization, even biomolecular machines like chaperonin proteins can be utilized as monomers.[93] The resulting nanotubular polymer responds to the binding and hydrolysis of

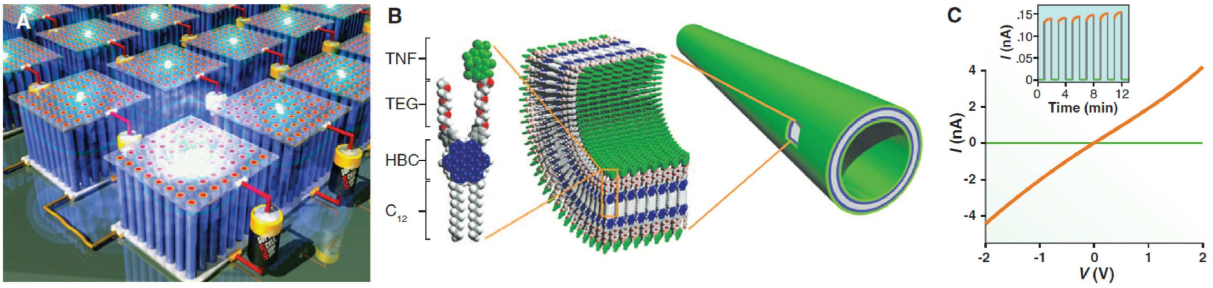

Figure 11. Hexabenzocoronene-based nanotubular supramolecular polymers as part of electronic devices; A) the cartoon of the device; b) the monomer and the supramolecular tubular aggregate; c) the I-V curves with the inset showing the switching behavior – adapted from Science.[47]

ATP, which results in depolymerization and therefore releasing guests.[94]

7. Comparison between Macromolecular and Supramolecular Polymers

In 2020, it is useful and historically fascinating to compare covalent or macromolecular polymers with their supramolecular counterparts. The insights obtained in the last 20 years have shown their remarkable resemblance. In many aspects, the two polymers behave completely similar, except the dynamic nature of the bonding of monomers within the polymers. Firstly, in both cases monomers are polymerized into long one-dimensional structures with lengths depending on the type of monomer and the process and mechanism of formation. While covalent macromolecules can be made with molecular weights beyond several million Daltons, the longest supramolecular polymers can exceed several microns. Secondly, different mechanisms of the formation (step/isodesmic versus chain/cooperative) are operative. A variety of homopolymers and copolymers as well as crosslinked three-dimensional structures have been synthesized even by supramolecular approaches. Polyesters and polyamides have their thermodynamic equilibrium between linear and cyclic structures. Likewise, most supramolecular polymers formed by the isodesmic mechanism are in the same equilibrium. At elevated temperatures, the kinetics of transesterification is very similar to the exchange dynamics of monomers in supramolecular polymers at lower temperatures. For cooperative supramolecular polymerizations, it is attractive to compare them with covalent chain polymerizations. However, some distinct difference are present as the kinetic stability of supramolecular polymers is limited to very limited. For supramolecular polymers with slow dynamics, i. e. kinetically very stable polymers, the resemblance with macromolecular polymers is striking again. Block copolymer synthesis and end-group as well as chain-length control are possible, however, examples are scars at present. Often cooperative polymerizations are under thermodynamic control, while covalent chain polymerizations are kinetically controlled. Finally, most striking are the observations made for (dynamic and static) helical macromolecules and chiral supramolecular polymers; almost every aspect – again except the dynamic behaviors of supramolecular polymers – is in great detail similar.

Despite all the similarities between macromolecular and supramolecular polymers, one aspect is strikingly different and that is the nature of the bonding that makes the polymer. The full spectrum and wealth of the fascinating properties as a result of the dynamic nature of supramolecular polymers has only recently been recognized. The notion that this dynamics can be tuned and biased at will by both external stimuli (like solvents) and internal conversions, is only one of the aspects that gives supramolecular polymers a bright future. These ideas have recently been explored to arrive at out-of-equilibrium systems and illustrate another new aspect of supramolecular polymer science; an emerging field that is only at its beginning.[95,96,97] Similarly, using supramolecular polymers to switch liquid-crystals is just one of other new features where the dynamics of the system is used.[98]

8. Perspective on Some of the Major Challenges

Remarkably, in the year that we celebrate the hundredth birthday of Staudinger's concept of macromolecules, it has become well accepted that polymers can also be formed through supramolecular polymerization of small molecules. In other words, polymers and macromolecules are not synonyms anymore. Many applications are under investigations and some of the major mechanistic insights are unraveled (*vide supra*), whereas many challenges remain in all areas of supramolecular polymer science and engineering. We are still far off from writing a book similar to Odian's "Principles of polymerization".[99] For the supramolecular homopolymerization, we have made enormous progress and many aspects are understood, both for the isodesmic and cooperative polymerizations. However this is not the case for copolymerization. Concepts to arrive at block copolymers under thermodynamic and kinetic controls are just emerging, but lack clear generality at present. Whereas chain-cappers for the isodesmic supramolecular polymers are easy to design, for highly cooperative and ordered polymers it is still a mystery.[100] Dynamics of the exchange of monomers from one polymer to the other is probably one of the most fascinating elements of ordered filaments in solution. This exchange can occur at the end of the chain or just by an escape from within the chain followed by an intercalation to enter another chain. It is still an open question whether this exchange occurs "one-by-one" at the molecular level or at the level of small assemblies of repeating units. Moreover, since these long supramolecular polymers do not possess structural integrity – certain parts are less ordered then others – it becomes even more fascinating to compare the exchange in these different parts. Next to chain ends, defects and highly-ordered parts of the chain can introduce points for exchange. With these challenges in mind, it becomes relevant to compare synthetic supramolecular polymers with biological ones, e. g. beta-amyloid and collagen filaments.[70] Although many of the concepts discussed in the present article have their parallels in natural supramolecular polymerizations, insights into the synthetic ones are still lagging behind the understanding of their biological counterparts.

In the last 30 years after the first report of a supramolecular polymer and the last 20 years after the first publications on supramolecular polymeric materials based on the one-dimensional assembly of small molecules, the field has grown into a very important new branch of polymer science. It has attracted numerous research activities in academia and industrial laboratories worldwide. New dynamic materials with a variety of anomalous properties are added to the field of materials engineering. Many applications in sustainability (easy processing and recycling), electronics, and medicine as well as cosmetics have become available. In all cases the modular approach in the assembly of multiple building blocks has opened new avenues to arrive at functional materials. Materials can be made that are self-healable, responsive, reorganizable and adaptive; all prospects that overreach those described in the first book on supramolecular polymers by Cifferi in 2005.[101]

In the decades to come, we expect a significant impact of supramolecular polymers in society based on comprehensive understanding of their basics and applications. In retrospect, these fundamental aspects will underpin that, 100 years after the Staudinger's publication, Ostwald, who supported the colloidal theory in the historic debate, turned out to be visionary to predict polymer materials without a macromolecular structure.

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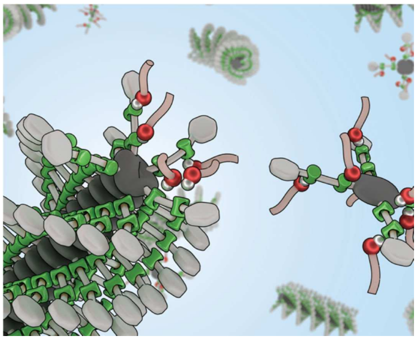

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