Advances in Polymer Science 268

Sebastian Seiffert *Editor*

Supramolecular Polymer Networks and Gels

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Aims and Scope

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Sebastian Seiffert
Editor

Supramolecular Polymer Networks and Gels

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ISSN 0065-3195 ISSN 1436-5030 (electronic)
Advances in Polymer Science
ISBN 978-3-319-15403-9 ISBN 978-3-319-15404-6 (eBook)
DOI 10.1007/978-3-319-15404-6

Library of Congress Control Number: 2015936665

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

Supramolecular polymer networks and gels consist of monomeric, oligomeric, or polymeric building blocks transiently and dynamically interconnected by non-covalent bonds. This mode of interconnection is responsible for the promising potential of these materials to serve as adaptive, self-healing, and stimuli-responsive coatings, elastomers, and scaffolds in both the life and materials sciences. To make this truly useful, it is necessary to achieve systematic and comprehensive understanding of the molecular-scale interactions and macromolecular-scale structures and dynamics of these networks and gels. Various efforts have been and are being made to achieve such understanding and to develop advanced functional soft materials. It is therefore a good time to review some of these activities; this volume aims to provide such a review. In the following chapters, several examples and achievements of recent and current research activities are given. Anthamatten reviews hydrogen-bonding interactions to form soft solid polymer-network structures and materials, including glasses, melts, and elastomers. Okay adds a perspective on the design, mechanics, and self-healing of hydrogels formed via hydrophobic interactions, with a particular emphasis on the role of surfactant micelles within the gels. The development of donor–acceptor – stacking interactions that serve as transient crosslinks in self-healable supramolecular polymer networks is discussed by Greenland and Hayes. Chau, Sriskandha, Thérien-Aubin, and Kumacheva highlight recent progress in the field of nanofibrillar supramolecular gels, discussing both synthetic and natural materials. Liu adds a particular view on the potential of cellulose and cellulose derivatives for the formation of chemical and physical gels and microgels, with a specific focus on supramolecular interactions within them. Finally, Pape and Dankers provide a review on supramolecular hydrogels of several kinds for use in the field of regenerative medicine.

I would like to take the chance to greatly thank all these colleagues for providing these deep and illustrative insights into their work and that of their peers. I believe

that the collection of contributions presented in this volume truly arcs from fundamental physical-chemical investigation to advanced development and use of supramolecular polymer networks and gels, which I expect to further evolve as a particularly promising and fascinating class of soft matter in the near future.

Berlin Sebastian Seiffert
April 2015

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Supramolecular Polymer Networks: Preparation, Properties, and Potential

Torsten Rossow and Sebastian Seiffert

Contents

Abstract Supramolecular polymer networks consist of macromolecules interconnected by transient, noncovalent bonds such as those through hydrogen bonding, transition metal complexation, hydrophobic interaction, ionic attraction, or π–π stacking. These networks form an extraordinarily useful class of soft, stimuli-sensitive materials. Although they assemble to strong materials under

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S. Seiffert (ed.), *Supramolecular Polymer Networks and Gels*, Advances in Polymer Science 268, DOI 10.1007/978-3-319-15404-6_1

favorable conditions, they are easily disassembled under other conditions. This ambivalent nature renders supramolecular polymer networks useful for applications in drug delivery, tissue engineering, self-healing, and shape-memory materials. These applications require a deep and comprehensive understanding of the physical chemistry of supramolecular networks, with a particular view to the complex interplay between their structure, dynamics, and properties. Approaches that have attempted to derive such knowledge are often based on investigations of supramolecular polymer networks in the melt or of supramolecular polymer networks swollen in organic media. These approaches are reviewed in the first part of this chapter. In the second part, we focus on the preparation and characterization of supramolecular hydrogels based on synthetic and natural precursors and reveal their utility and potential in life science applications.

Keywords Supramolecular polymer gels • Stimuli-responsive materials • Noncovalent interactions • Supramolecular network dynamics • Self-assembly

1 Supramolecular Interactions

"*Supramolecular chemistry may be defined as 'chemistry beyond the molecule', bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces*." This definition was given by Lehn in 1987 [1] when he received the Nobel prize together with C. J. Pedersen and D. J. Cram for their work on host–guest chemistry. Since then, supramolecular chemistry has gained increasing attention and developed into an important, broad, and active field of research [2–4]. Today, research on supramolecular chemistry can be subdivided into several categories: host–guest complexes [5–7], self-assembled architectures [8, 9], supramolecular polymers [10–14], supramolecular gels [15–18], and supramolecular polymer networks [19, 20].

The term "supramolecular polymer" refers to a polymer built of monomeric units associated through directional noncovalent physical interactions. Supramolecular gels typically consist of low molecular weight precursors that self-assemble into three-dimensional networks through noncovalent interactions; these materials are often brittle and hard to customize. In contrast, supramolecular polymer networks consist of covalently joined macromolecular building blocks (polymers) that are functionalized with motifs that can bind to each other through noncovalent interactions such as hydrogen bonding [21–23], transition metal complexation [11, 24, 25], hydrophobic interaction [26], ionic attraction [10], or π–π stacking [27–29], serving to assemble the polymer chains into a network. Noncovalent interactions strongly vary in their strength, as shown in Fig. 1. As a result, supramolecular polymer materials can be tuned to exhibit different mechanical properties by custom use of these interactions for polymer cross-linking.

Supramolecular polymer networks combine the characteristics of chemical and physical networks and can be tailored to specific needs through the use of macromolecular building blocks. Although they form strong materials under favorable

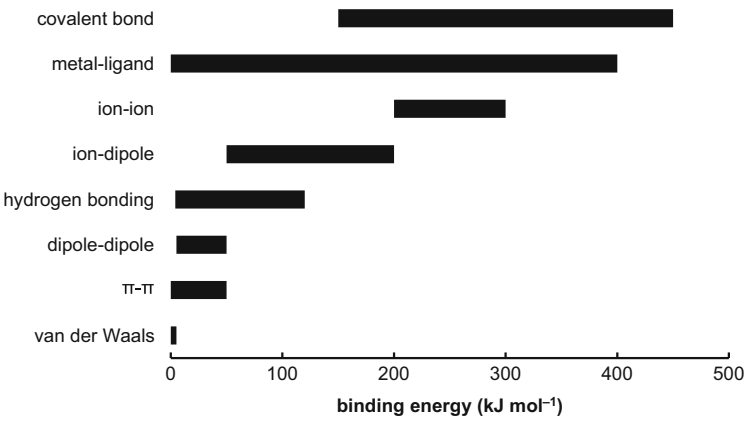

Fig. 1 The most important noncovalent interactions along with their typical range of binding strength, in comparison with covalent bonds [30]

conditions, they are easily de-cross-linked under other conditions. Physically associating motifs can be divided into those that associate with one another in a self-complementary fashion and those that require a different complementary motif to associate in a heterocomplementary fashion. The latter approach is useful for accessing more sophisticated materials because, in this approach, the strength of cross-linking is tunable by various complementary motifs. Different design principles can serve to build such supramolecular networks, as illustrated in Fig. 2. In one principle, linear chains functionalized with supramolecular linkable motifs at both chain ends are cross-linked if these motifs form associative nodes with a functionality greater than two (Fig. 2a). In a second principle, systems that form supramolecular linear chains can be cross-linked by entanglement of the polymer chains or by phase separation through lateral interactions of the transient cross-links, including stacking, clustering, or crystallization (Fig. 2b). In a third principle, the supramolecular motifs are attached as side chains to a polymer backbone, resulting in polymer cross-linking even if the supramolecular motifs assemble in a bivalent fashion. If heterocomplementary motifs are used, cross-linking is achievable by addition of low molecular weight cross-linking agents to the supramolecular cross-linkable polymers (Fig. 2c) or by using a second polymer functionalized with a complementary supramolecular motif (Fig. 2d). The supramolecular motifs can be introduced to the side chains after synthesis of the polymer backbone in a post-polymerization step. As an alternative, monomers that contain the supramolecular motifs beforehand can be polymerized in a suitable chain- or step-growth process.

Because of their transient and reversible cross-linking, supramolecular polymer networks are responsive [4] to external stimuli such as variation in temperature [31], pH [32], polarity of the solvent [33], redox reactions [34], and competitive ligation [35]. This tunability makes them useful for a plethora of applications. They can be used as drug delivery systems [36] and as matrixes in tissue engineering [37]. Drugs and cells can be encapsulated and protected within these materials and

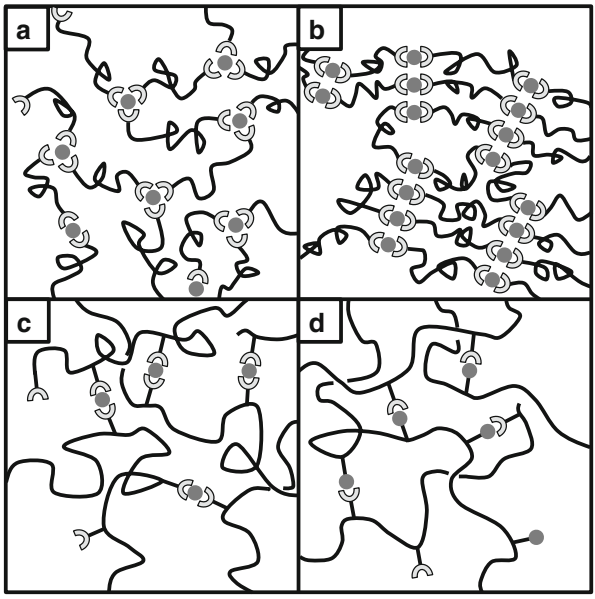

Fig. 2 Different design principles for preparation of supramolecular polymer networks by heterocomplementary interactions. Cross-linking of end-capped linear chains by (**a**) associative nodes with a functionality higher than two or (**b**) additional lateral chain interactions. As an alternative, side-chain functionalized polymer chains can associate by (**c**) low molecular weight cross-linkers or (**d**) mutual heterocomplementary polymer–polymer binding

afterward released on demand at a targeted site of action. Furthermore, supramolecular polymer networks often have self-healing properties [38, 39]; after rupture, supramolecular bonds can re-associate when brought into contact, thereby healing the material. In addition, the combination of supramolecular and covalent cross-linking gives rise to shape-memory materials [40].

Many different polymeric precursors can be used to prepare supramolecular polymer networks, including synthetic polymers, natural polymers, and hybrids of both. In approaches that serve to derive fundamental physical–chemical understanding of supramolecular polymer networks, synthetic precursors are mostly used because chemical modification allows them to be tailored as desired. When it comes to further tailoring of supramolecular polymer materials for practical applications in the biological area, a popular class of precursor polymers are those that are water soluble, including poly(ethylene glycol) (PEG) [41, 42], poly(vinyl alcohol) (PVA) [43–45], and polyglycerol [46–48]. However, several other synthetic precursors are only soluble in organic solvents. In addition, many supramolecular polymer networks are labile in water because many binding motifs do not form interactions strong enough to withstand competitive hydrogen bonding. Hence, popular alternatives to fully synthetic supramolecular polymer gels are natural polymer gels [49], such as those based on alginate [50–53], gelatin [54], or chitosan [55], which can form hydrogels even without chemical modification. These materials are biocompatible, bioavailable, biodegradable, and cheap, which makes them ideal candidates for life science applications [56]. However, natural polymers also have disadvantages [57]: they differ in their composition from batch to batch because they are harvested from living organisms [58, 59], the production of large volumes

of natural polymers is limited, and they cannot be tailored according to the demand of different applications because their properties are determined by the species that produce them [60]. As a result, the combination of synthetic and natural polymeric precursors in hybrid networks often presents an excellent compromise.

The following sections describe the preparation and characterization of supramolecular polymer networks, particularly emphasizing their physical–chemical features with regard to the type and strength of physical chain cross-linking and the resulting macroscopic material properties. Furthermore, recent work on the formation and characterization of supramolecular hydrogels based on synthetic and natural precursors is summarized with a focus on their application and potential in biomedicine.

2 Supramolecular Polymer Networks and Organogels

2.1 Hydrogen Bonding

Hydrogen bonding plays a crucial role in many biological processes such as DNA base pairing, ligand–receptor binding, enzyme catalysis, and protein folding. It has also become the most widely used noncovalent interaction for the synthesis of supramolecular polymers and reversibly cross-linked polymer networks [61–66]. This is not due to the binding strength of hydrogen bonds, which is just 4–120 kJ mol^{-1} (Fig. 1), but is a result of their strong directionality and versatility.

Nernst described weak interactions between molecules containing hydroxyl groups in 1892 [67] but the term ‘hydrogen bond’ was first introduced by Bernal and Huggins in 1935 [68, 69]. Hydrogen bonds connect atoms X and Y that have electronegativities larger than that of hydrogen. The XH group is generally referred to as the ‘proton donor’ (D), whereas Y is called the ‘proton acceptor’ (A) [61]. An increase in the dipole moment of the X–H bond and the electron lone pair on atom Y entails an increase in the hydrogen-bonding strength. For the strength of hydrogen-bonded complexes, however, the strength of a single hydrogen bond is less crucial than the number of hydrogen bonds within a hydrogen-bonding motif. When acting together in a cooperative fashion, hydrogen bonds become much stronger than their simple numerical sum. The binding constant of the DNA base pair guanine–cytosine (Fig. 3a), which contains three hydrogen bonds, is two to three orders of magnitude larger than that of the adenine–thymine complex that contains just two hydrogen bonds [63]. In the guanine–cytosine complex, not only the higher number of primary hydrogen bonds plays an important role, but also secondary interactions arising as a result of the particular arrangement of neighboring donor and acceptor sites, as shown in Fig. 3a. Complexes between the ADA–DAD motifs exhibit an association constant of around 10^2 M^{-1} in chloroform, whereas DAA–DDA complexes exhibit binding constants of 10^4 M^{-1} [70]. AAA–DDD arrays even have association constants higher than 10^5 M^{-1}. Jorgensen and

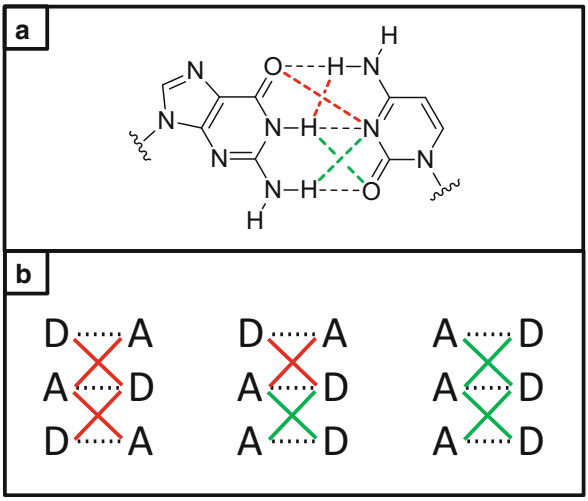

Fig. 3 Secondary hydrogen-bonding interactions. Attractive interactions are marked *green*, and repulsive interactions are marked *red*. (**a**) Guanine–cytosine complex in the DNA strand. (**b**) Possible secondary interactions in different triple hydrogen-bonding motifs

colleagues [71, 72] attributed this effect to differences in secondary interactions between these motifs. Diagonally opposed sites electrostatically repel each other when they are of the same kind, whereas contrary sites attract each other. Hence, the ADA–DAD complex has four repulsive secondary interactions, the DAA–DDA complex has two repulsive and two attractive interactions, and the AAA–DDD complex has four attracting interactions, as visualized in Fig. 3b.

Calculations by Schneider reveal that the arrangement of several hydrogen bonds can be modeled by a linear correlation, in which primary interactions contribute -8.0 kJ mol^{-1} to the complex stability, whereas secondary attractive or repulsive interactions contribute ± 2.9 kJ mol^{-1}[73]. In addition to secondary interactions, the pre-organization, intramolecular hydrogen bonding, tautomerization, and electronic substituent effects of the hydrogen-bonding motifs significantly contribute to the cooperative effect [63]. For pre-organization, a rigid aromatic framework is often used that presents multiple hydrogen-bonding sites wherein an entropy cost has to be paid only for the formation of the first hydrogen bond. In the case of amides, however, which are able to rotate and often stay in the preferred *trans*-confirmation in the uncomplexed form, the amide bond has to rotate to the *cis*-confirmation for complex formation and needs to be fixed in this position, which costs entropy. An overview of hydrogen-bonding motifs discussed in this chapter is given in Scheme 1.

In a pioneering application, the formation of thermoplastic elastomers cross-linked by hydrogen bonding was explored by Stadler and coworkers in 1986 [74–76]. In this work, nonpolar polybutadienes with narrow molecular weight distributions were modified with urazole side groups. Hydrogen bonding between the highly polar urazole groups gives rise to the formation of thermoreversible elastomeric networks. The rheological properties of these networks were investigated in the melt. No rubbery elastic equilibrium network modulus is observed due to the fragility of the transient hydrogen-bonding linkages. At low frequencies,