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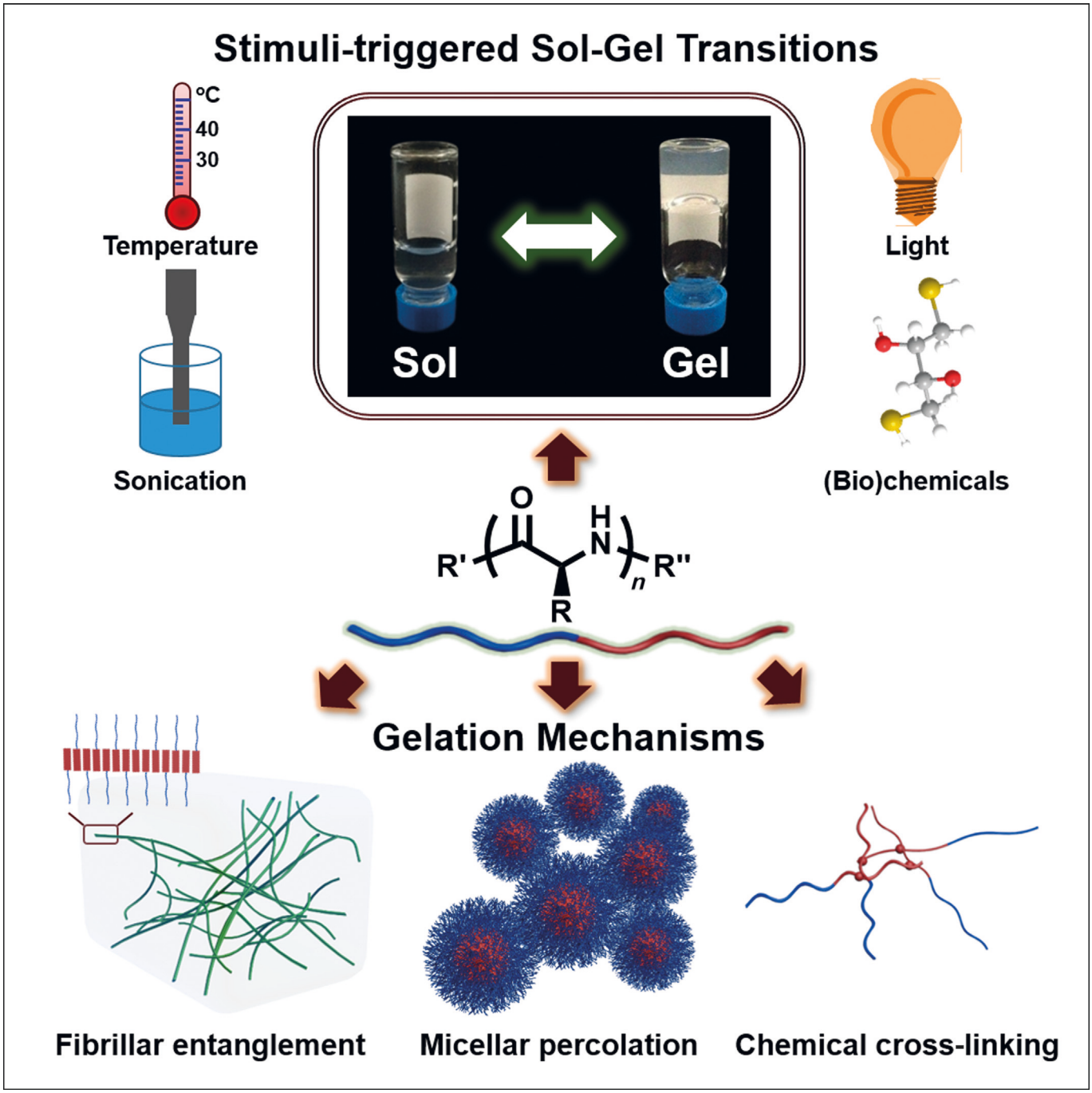
Stimuli-Triggered Sol–Gel Transitions of Polypeptides Derived from α-Amino Acid *N*-Carboxyanhydride (NCA) Polymerizations

Xun He, Jingwei Fan, and Karen L. Wooley*[a]



Abstract: The past decade has witnessed significantly increased interest in the development of smart polypeptide-based organo- and hydrogel systems with stimuli responsiveness, especially those that exhibit sol–gel phase-transition properties, with an anticipation of their utility in the construction of adaptive materials, sensor designs, and controlled release systems, among other applications. Such developments have been facilitated by dramatic progress in controlled polymerizations of α-amino acid *N*-carboxyanhydrides (NCAs), together with advanced orthogonal functionalization techniques, which have enabled economical and practical syntheses of well-defined polypeptides and peptide hybrid polymeric materials. One-dimensional stacking of polypeptides or peptide aggregations in the forms of certain ordered conformations, such as α helices and β sheets, in combination with further physical or chemical cross-linking, result in the construction of three-dimensional matrices of polypeptide gel systems. The macroscopic sol–gel transitions, resulting from the construction or deconstruction of gel networks and the conformational changes between secondary structures, can be triggered by external stimuli, including environmental factors, electromagnetic fields, and (bio)chemical species. Herein, the most recent advances in polypeptide gel systems are described, covering synthetic strategies, gelation mechanisms, and stimuli-triggered sol–gel transitions, with the aim of demonstrating the relationships between chemical compositions, supramolecular structures, and responsive properties of polypeptide-based organo- and hydrogels.

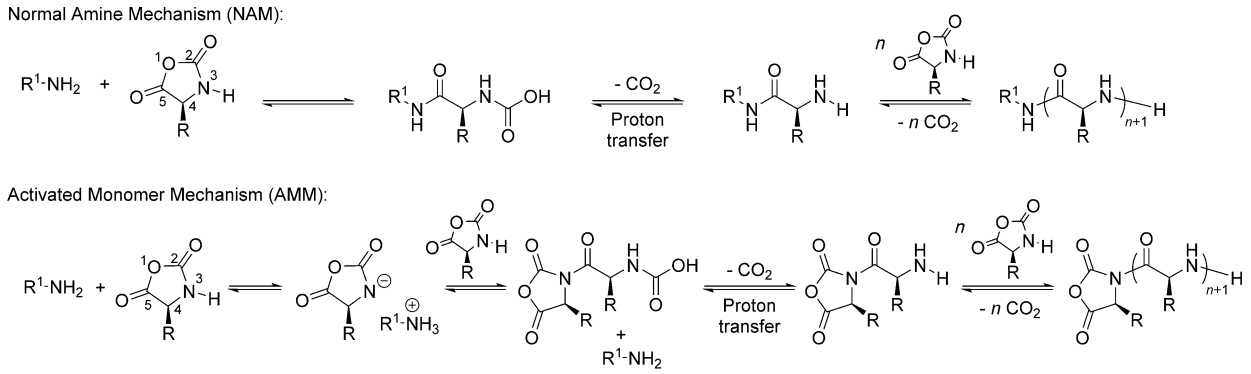
1. Introduction

Smart gels contain medium (typically liquid) in a matrix of physically and/or covalently cross-linked solid network, and show controllable chemical structure changes or physical property variations through treatment with certain stimuli, which include, but are not limited to, changes of environmental factors (temperature, mechanical force), exposure to electromagnetic fields (light, magnetic field), and subjection to (bio)chemical species (protein, acid/base, redox agent).[1] A highly attractive feature of most gel materials is that they require only a small fraction of gelators to promote molecular-to-macroscopic amplifications in response to a stimulus. In the last two decades, significant efforts have been devoted to the research of smart gels owing to their capability to respond to stimuli rapidly, the versatility to assemble into specific nano- and/or microstructures in various environments, and the ability to exhibit changes in macroscopic characteristics, such as switches between liquid and gel states, also named sol–gel phase transitions.[2] Gels with stimuli-triggered sol–gel transitions, through construction and deconstruction of the gel networks by either covalent or noncovalent interactions, have found extensive applications in controlled drug release,[3] tissue engineering,[4] selective sensing,[5] and photolithography fields.[6] The drastic difference in the physical properties between sol and gel states, and the rapid switch of sol–gel transitions have rendered smart gels as potential materials for applications that require both sol- and gel-type behavior during different stages of operation.[7] The stimuli-triggered sol–gel transition process enables the localization and breakdown of the soft gelation materials with spatial and temporal precision, which is of great significance for controlled material fabrication, implantation, and degradation.

Among the smart stimuli-responsive gelators, synthetic polypeptides are of great interest toward biomedical applications owing to their innate biocompatibility and biodegradability, and have been widely investigated for their gelation mechanisms and responsive sol–gel transition behavior for the following reasons.[8] First, compared with conventional solid-phase peptide synthesis, ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCAs) has provided a more practical synthetic approach to prepare well-defined polypeptides in scalable quantities with controllable polymerization rates, predictable molecular weights, narrow molecular weight distributions, and unchanged amino acid chirality.[9] In addition, depending on the side-chain moieties, polypeptides can adopt unique ordered conformations, including α helices and β sheets, which can be controlled through molecular design and tuned through triggers from external stimuli, with correlations between the conformational switch of secondary structures and the sol–gel phase transition.[10] Moreover, side-chain functionalities with diverse responsive components can be readily incorporated into polypeptides; this contributes to the exceptional versatility of natural and synthetic side-chain-functionalized monomer species and highly efficient orthogonal functionalization techniques, for pre- and post-polymerization modifications, respectively.[11]

Recently, a number of reviews have been published that focused on the subjects of synthetic methodologies, stimuli-responsive properties, and biomedical applications of polypeptide-based materials.[9b,10a,11a,12] Herein, the most recent advances in synthetic approaches for NCA ROPs are briefly captured, followed by highlights and descriptions of diverse gelation mechanisms and categories of stimuli-triggered sol–gel transitions, with the aim of providing a tutorial on the chemical composition, supramolecular structure, and responsive proper-

[a] *X. He, J. Fan, Prof. K. L. Wooley*
Departments of Chemistry, Chemical Engineering and Materials Science and Engineering
Laboratory for Synthetic-Biologic Interactions
Texas A&M University, 3255 TAMU
College Station, TX 77842 (USA)
E-mail: wooley@chem.tamu.edu
ORCID(s) from the author(s) for this article is/are available on the WWW under http://dx.doi.org/10.1002/asia.201500957.



Scheme 1. NAM and AMM pathways for ROPs of NCAs.

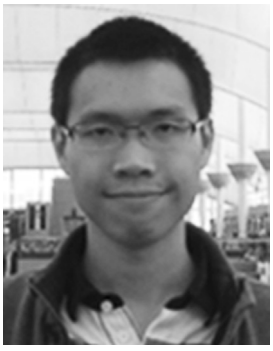
ty relationships for the rational design of polypeptide gel materials.

2. Polypeptide Syntheses from NCA ROPs

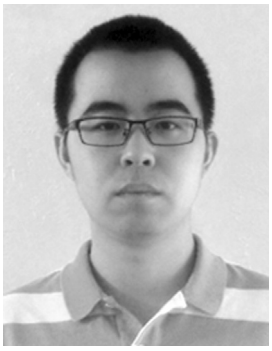
Amino acid NCAs have been studied for over 100 years, since the reports by Leuchs in and shortly after 1906.[13] In comparison with conventional solid-phase peptide synthesis, the ROP of NCAs is a more economical and practical synthetic approach for the preparation of polypeptides and peptide hybrid polymeric materials, especially for the synthesis of polypeptides with over 100 repeat units.[9a,12b,c,14] NCA ROP can be initiated by a range of nucleophiles and bases. Depending on the initiators used in the polymerization, two widely accepted pathways of NCA polymerizations are normal amine mechanism (NAM) and activated monomer mechanism (AMM; Scheme 1).[12c,14a] In NAM, polymerization is generally initiated by nonionic initiators, which exhibit more nucleophilicity than basicity, such as primary amines, alcohols, and water. During polymerization, the initiator acts as the nucleophile to attack the carbonyl group at 5-C to open the ring structure of the NCA monomer. After the release of CO_2, the reproduced amine chain end will continue to serve as a nucleophile to attack the carbonyl group of another NCA monomer to propagate polymer growth. In contrast, AMM involves the initiator acting as a base rather than as a nucleophile, which deprotonates the nitrogen (3-N) in the NCA monomer and results in the formation of a corresponding anion. This anion then acts as a nucleophile to attack the carbonyl group at 5-C of another NCA monomer, leading to ring opening and further chain propagation in the same manner as that in NAM. Owing to the relatively slower initiation step, in comparison with propagation in AMM, polymerizations following the AMM pathway commonly yield less-controlled and ill-defined polypeptides.[14a] Of course, these two mechanistic treatments are at extremes, with all processes involving equilibria and each in competition.

Owing to the coexistence of these two polymerization pathways during NCA ROPs, it is often problematic to synthesize high-molecular-weight polypeptides with controlled structures and varied architectures. Over the past century, significant ad-

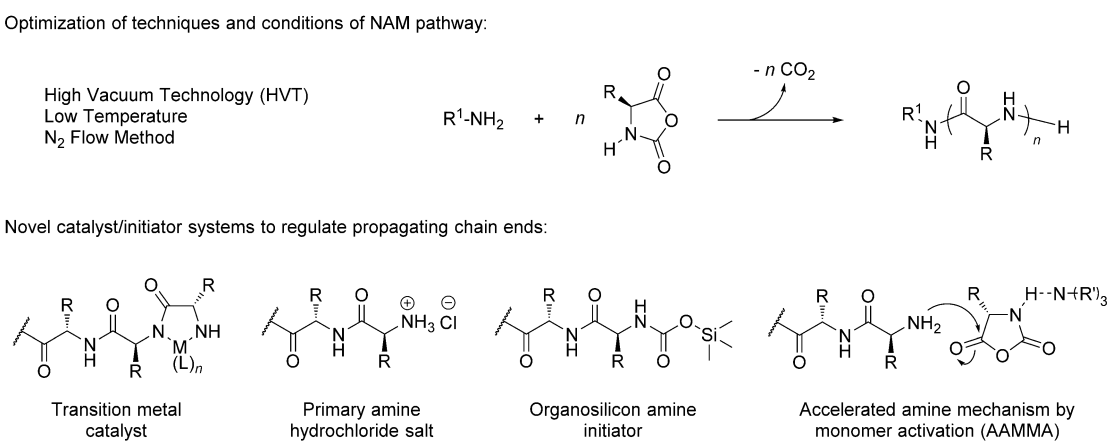
Xun He received his B.S. in chemistry from Wuhan University (P.R. China) in 2012. In the same year, he joined the group of Prof. Karen L. Wooley at Texas A&M University to pursue his Ph.D. degree. His current research focuses on the development of polymeric smart hydrogels for photoprintable materials.



Jingwei Fan is currently a Ph.D. candidate under the direction of Prof. Karen L. Wooley in the Department of Chemistry at Texas A&M University. He received his B.S. in materials chemistry from Nankai University (P.R. China) in 2011. His research focuses on the development of novel polypeptide materials toward nanomedical applications.



Karen L. Wooley received a B.S. in chemistry from Oregon State University in 1988 and a Ph.D. in polymer/organic chemistry from Cornell University in 1993. She began as an Assistant Professor at Washington University in St. Louis in 1993, was promoted in 1999 to Full Professor, and was installed as a James S. McDonnell Distinguished University Professor in Arts & Sciences in 2006. In 2009, she relocated to Texas A&M University, undertaking a position as the W. T. Doherty-Welch Chair in Chemistry, and she was awarded the title of University Distinguished Professor in 2011. Her research areas include the synthesis and characterization of degradable polymers, unique macromolecular architectures and complex polymer assemblies, and the design and development of well-defined nanostructured materials.



Scheme 2. Recent advances for controlled ROPs of NCAs, including optimization of techniques and conditions, and the development of novel catalyst/initiator systems.

vances have been made toward NCA ROPs to synthesize well-defined polypeptides, by preventing, or at least limiting, the AMM pathway during polymerization.[12b,c] The AMM pathway can be suppressed by optimization of experimental techniques and reaction conditions, while maintaining the utilization of primary amines as initiators (Scheme 2).[12c,15] These approaches are attractive because many primary amine initiators are commercially available, and there is no need for the use and removal of a catalyst. In 2004, the group of Hadjichristidis applied HVTs to purify NCA monomers and conduct polymerizations with intermittent removal of CO_2 generated during the reaction.[16] A detailed study of the kinetics indicated rapid and controlled polymerization by NAM with efficient inhibition of AMM. The controlled living polymerization under high vacuum was also confirmed by Messman and co-workers.[17] In 2004, Vayaboury et al. reported another innovative approach to eliminate side reactions by systematically studying hexylamine-initiated polymerizations of N^{ε}-trifluoroacetyl-L-lysine NCA as a function of temperature.[18] By lowering the reaction temperature from 20 to 0 °C, the living amine chain ends increased dramatically from 22 to 99%, as analyzed by a combination of size exclusion chromatography (SEC) and nonaqueous capillary electrophoresis (NACE). To overcome the drawback of long polymerization times at low temperature, the group of Heise investigated NCA ROPs of various NCA monomers by combining high-vacuum and low-temperature techniques, which not only promoted the polymerizations in a controlled manner, but also significantly shortened the polymerization times.[19] Most recently, a facile method to prepare well-defined polypeptides by applying continuous nitrogen flow during polymerization was developed by Zou et al. in 2013 and confirmed soon by Cui et al. in 2014.[20] The removal of CO_2 from the reaction mixture drove the equilibrium from the carbamic acid intermediate toward the terminal primary amine, which significantly accelerated the polymerization rate, and also suppressed side reactions, such as AMM, as revealed by successful chain-extension experiments and diblock co-polypeptide syntheses.

In addition to the optimization of experimental techniques and reaction conditions, several novel catalyst and initiator systems for regulating propagating chain ends have been developed in the past two decades (Scheme 2).[12c,15a] In 1997, Deming reported the first living polymerization of NCA monomers by employing transition-metal complexes as active species to undergo oxidative addition with NCA monomers, which prevented deprotonation of the NCA nitrogen.[21] By using zero-valent nickel and cobalt initiators (i.e., $[Co(PMe_3)_4]$, and [Ni(bpy)(cod)] (bpy = 2,2′-bipyridine, cod = 1,5-cyclooctadiene), high-molecular-weight polypeptides with well-defined homo-, di-, tri-, and multiblock architectures were obtained. In 2003, another living NCA ROP was reported by using a primary amine hydrochloride salt as the initiator.[22] The primary amine hydrochloride significantly decreased the basicity of the initiator and inhibited the AMM pathway.[23] However, the nucleophilicity of free amines was also reduced in the formation of the hydrochloride salts, which resulted in long polymerization times. In 2007, the group of Cheng reported organosilicon-mediated living NCA polymerization through a group transfer mechanism.[24] This novel initiator significantly reduced polymerization times and afforded precise control over polypeptide structures, which resulted from the unexpected formation of trimethylsilyl carbamate (TMS-CBM) end groups in both initiation and propagation steps. In later work, other N-TMS amine based initiators were also developed to introduce functional groups for further modification, while maintaining the living features of NCA ROPs.[25] Most recently, Zhao et al. developed a fast and living NCA polymerization methodology by the incorporation of both primary and secondary or tertiary amines into one initiation system through an accelerated amine mechanism through monomer activation (AAMMA).[26] Instead of competition between polymerizations initiated from diverse amines, the secondary or tertiary amines activated NCA monomers through hydrogen bonding to facilitate the initiation and propagation steps of primary-amine-initiated polymerizations, resulting in well-defined polypeptides.

3. Polypeptide Gelation Mechanisms

The formation of cross-linking sites by either physical interactions or chemical cross-linkers is one of the most important factors for the creation of three-dimensional networks to entrap organic solvents or aqueous media in a gel.[27] Commonly, physical cross-linking interactions include relatively strong supramolecular interactions, such as hydrogen bonding, hydrophobic interactions, π–π stacking, host–guest interactions, and metal–ligand interactions.[28] For example, driven by inter- and intramolecular hydrogen-bonding interactions, polypeptides can supramolecularly assemble into nanofibril and/or nanoribbon structures with one-dimensional stacking of polymers or polymer aggregations, including α-helical and β-sheet secondary structures.[3b,21b,29] Stimuli-triggered construction of the nanostructures in polypeptide materials, or changes to the conformations between secondary structures, would result in gel formation. Another vital factor to consider for gelation is the solvophilic–solvophobic balance. Owing to nano- and/or microphase separation derived from supramolecular assembly of polypeptides, a delicate solvophilic–solvophobic balance should be achieved in polypeptide-based gels. Interactions that are strong enough to break this balance would cause either gel breaking into a viscous liquid or polymer precipitation.

For polypeptide-based gelators that contain at least one polypeptide block segment, secondary structures are considered to be a remarkable driving force for gelation. To construct supramolecularly assembled gels, the alignment of secondary structures, including α helices and β sheets, into one-dimensional nanofibril or -ribbon structures have been investigated widely, together with incorporation of another block segment, which commonly adopts random-coil conformations, to increase the solubility of supramolecular assemblies and balance the solvophilic–solvophobic interactions (Figure 1 a).[29a,c–e] For

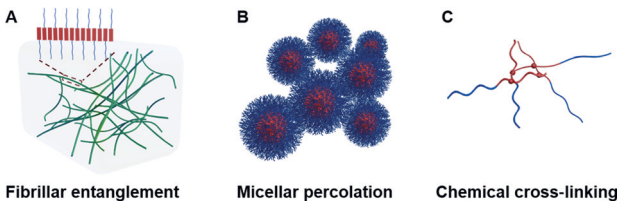


Figure 1. Schematic illustrations of polypeptide gelation mechanisms through fibrillar entanglement, micellar percolation, and chemical cross-linking.

example, Kim et al. reported poly(ferrocenylsilane)-*block*-poly(γ-benzyl-L-glutamate) (PFS-*b*-PBLG) as an organogelator in toluene; this originated from the monolayer one-dimensional stacking of the α-helical polypeptide segments (PBLG) into nanoribbons, as driven by the dipolar π–π stacking of phenyl groups on the side chains of PBLG, which further entangled physically to construct networks for gelation (Figure 2).[29a] The PFS block segment could be replaced by polystyrene (PS) and poly(ethylene glycol) (PEG) and similar gelation processes were observed; these resulted from the high solubility of all three

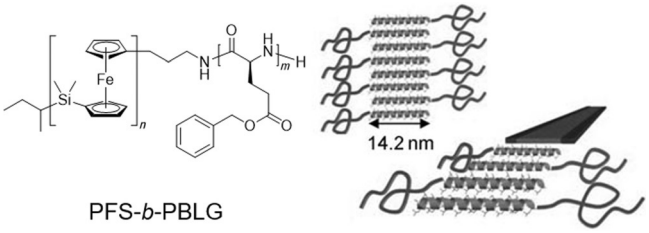


Figure 2. A schematic representation of the nanoribbon formed in PFS-*b*-PBLG toluene gel. Adapted from ref. [29a]. Copyright 2005 Wiley-VCH.

polymers in toluene when possessing random-coil conformations. Owing to the significant roles of secondary structures in the gelation process of polypeptide-based materials, the gelation property can be readily tuned by control over the secondary structures through structural modifications, such as tuning of the stereochemistry of polypeptides, varying the block lengths of solvophilic and -phobic segments, and introducing other moieties that are capable of hydrogen bonding or other supramolecular interactions into the gelation systems. Compared with polypeptides derived from L-amino acids, polypeptides from *rac*-amino acids typically could not undergo gelation or required much higher concentrations for gelation.[30] In the range of suitable solvophilic–solvophobic balance, longer solvophobic segments would induce stronger interactions in the nano- and/or microphase domains, which enhanced the gel-forming ability and gel strength.[31] In 2011, Jang et al. reported a poly(ethylene glycol)-*block*-poly(alanine)-*graft*-chitosan (PEG-*b*-PA-*g*-CS) with extensive intermolecular hydrogen bonding from the protonation of chitosan in an acidic environment to improve the gel-forming ability.[32a]

In the last decade, several groups have reported reverse thermal gelation from PEG-*block*-polypeptide diblock copolymers, which underwent a thermally induced sol-to-gel transition with an increase in temperature.[3b,33] Depending on the secondary structures formed in the polypeptide segment domains, two gelation mechanisms were proposed for this reverse thermal gelation. For polypeptides with β sheets dominating the secondary-structure populations, the polypeptide block segments assembled supramolecularly into nanofibril or -ribbon structures from one-dimensional stacking of polypeptides, whereas PEG possessed random-coil conformations in aqueous solution.[33a,d] With an increase in temperature, dehydration of PEG altered the hydrophilic–hydrophobic balance toward the hydrophobic direction. At the same time, the hydrophobic core was stabilized by strengthening the secondary structures from the polypeptides owing to a smaller packing distance from the shrinkage of PEG. Also, dehydration of the PEG block upon increasing the temperature enhanced physical cross-linking between the hydrophobic domains through stronger hydrophobic interactions. A further increase in temperature (ca. 60 °C) shifted the hydrophilic–hydrophobic balance out of the gelation range, which resulted in the precipitation of polymer from the mixtures. On the other hand, for polymers with more α-helical components in the polypeptide domains, micellar structures were often observed for amphiphilic block copolymers, in which the polypeptides assembled

into the core and PEG constructed the shell domain.[30a,33e] With an increase in temperature, dehydration of PEG enhanced the hydrophobic interactions and led to aggregation and close packing of micelles for the creation of percolating gel networks (Figure 1 b).[34]

In addition to the above mechanisms related to the formation of physically cross-linked nanofibril/-ribbons or aggregated micelles, chemical cross-linking between functional side chains of polypeptides enables gel formation and also introduces novel stimuli-responsive properties (including photo, pH, and redox), as discussed in Section 4 (Figure 1 c).

4. Stimuli-Triggered Sol–Gel Transitions

4.1. Unique Responsive Behavior by Assembly or Hydrolysis of Polypeptides

Unique to polypeptide-based gelator systems are sol–gel transitions that result from assembly or disassembly of polypeptide domains owing to changes in interactions between their secondary structures and/or degradation of the backbones as a result of the hydrolysis of amide bonds upon treatment with enzymes. This assembly and degradation behavior commonly correlated with the stimuli, including a change in temperature, exposure to mechanical force, and treatment with enzymes, which is discussed at the beginning of this section.

4.1.1. Temperature

Heat-Induced Gel-to-Sol Transitions

Gel-to-sol transitions resulting from an increase in temperature have been observed extensively in gelators derived from natural or artificial proteins. For this type of responsive phase transition, a renowned natural protein example is gelatin, which is commonly used as a gelling agent in the food industry. The hydrogelation mechanism of gelatin may be attributed to physical network formation that results from the coil-to-helix transition of protein chains in response to a decrease in temperature.[35] In terms of artificial proteins, notable examples are the proteins that contain leucine zipper domains, which may create hydrophobic interhelical interfaces that strengthen the interchain interactions.[36]

For polypeptide-derived gelators synthesized by NCA ROP, one of the most popular components is PBLG because of its capability to adopt a rigid α-helical conformation. This stiff conformation showed unique solution behavior, such as nematic liquid-crystalline ordering, which contributed to the thermoreversible gelation of PBLG-containing gelators in α-helicogenic solvents (e.g., toluene and benzyl alcohol).[37] For example, in 2012, the group of Mezzenga reported a triblock copolymer, PBLG-*block*-polydimethylsiloxane-*block*-PBLG (PBLG-*b*-PDMS-*b*-PBLG), which displayed thermoinduced gel-to-sol behavior in toluene (Figure 3).[38] The rods (derived from the α-helical PBLG components) and the coils (derived from PDMS domains) assembled into nanofibrils, with rods densely packed in the center of the fibrils, of which the thickness was tunable through control of the PBLG block length. Because identical

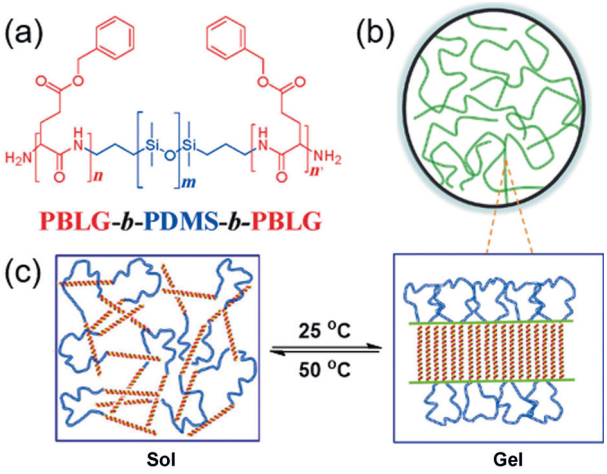


Figure 3. a) Molecular structure of PBLG-*b*-PDMS-*b*-PBLG. b) An illustration of nanofibril formation. c) Schematic representation of nanofibril formation or disruption at lower or higher temperature, respectively. Adapted from ref. [38]. Copyright 2012 American Chemical Society.

FTIR spectra were collected at 25 (gel state) and 50 °C (sol state), the heat-induced gel-to-sol transition was attributed to an increased solubility of the PBLG block in toluene at higher temperature.

Thermoinduced reversible gel-to-sol transitions were also observed in polypeptide gelators that formed β sheets. In 2013, we reported a series of PEG-*block*-poly(DL-allylglycine) (PEG-*b*-PDLAG) organogels, of which organogelation was proposed to result from the supramolecular assembly of peptide blocks into β-sheet-driven polymeric ribbons in a monolayer fashion.[29d] Gel melting was observed when the temperature was increased to the sol–gel transition temperature (T_{gel}), which was tunable by varying the polymer block lengths or solvents, whereas transparent gel recovery was achieved after several hours at room temperature. This gelator displayed an ultralow (*ca.* 0.1 wt%) critical gelation concentration (C_{gel}) in *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and methanol, although the peptide domains were constructed from racemic monomers.

Thermoreversed Gelation

An aqueous system that undergoes a sol-to-gel transition as the temperature increases is defined as a thermoreversed gelation system, which has attracted intense interest for its potential to deliver therapeutic molecules locally through minimally invasive administration. Owing to the capability of tuning the gelation temperature close to human physiological temperature, much attention has been paid to applying this reverse thermal gelation toward injectable biomedical applications. By this approach, it is expected that drugs or cells can be mixed into aqueous solutions of the polymer at lower temperature, such as room temperature. After being injected into the target site, the increase in temperature (for example, the change to human physiological temperature, 37 °C) triggers gel formation and promotes the cohesion of the mixture, which can act as a drug-release system or a cell-growth matrix.

From a synthetic standpoint, one popular design for a thermoreversed hydrogelator is to construct a hybrid PEG-*b*-peptide copolymer, for which the PEG block dehydrates and the peptide block displays an increased β-sheet content, with increasing temperature. For instance, in 2008 and 2009, the group of Jeong reported the incorporation of PEG, oligo(propylene glycol) (OPG), and oligopeptides into a series of multiblock amphiphilic hydrogelators, in which the two end-capped oligopeptide blocks were composed of oligo(alanine) or statistical oligopeptides of alanine and phenylalanine.[31a,39] As heat was applied to these polymer sols, the secondary structures of two oligopeptide end blocks changed from random coils to β sheets, as confirmed by circular dichroism (CD) spectroscopy, whereas the central PEG and OPG blocks dehydrated. Both the heat-induced formation of β sheets and block dehydration were anticipated to reinforce the interactions of the amphiphilic polymers to form a percolating network, which resulted in gelation over macroscale dimensions.

Analogous to the design from the group of Jeong, more PEG-*b*-β-sheet peptides with thermoreversed gelation behavior and mechanisms were reported by the groups of Heise,[33a] Chen,[33b] Li,[33c] and ours.[33d] As an illustration, for the oligo(DL-allylglycine)-*block*-PEG-*block*-oligo(DL-allylglycine) (ODLAG-*b*-PEG-*b*-ODLAG) triblock structure synthesized by us, the reversible macroscopic sol-to-gel transitions were correlated with the transformation of nanostructural morphologies, with spherical aggregates observed in the sol state and fibrillar structures in the gel state (Figure 4). Upon heating, the spherical aggregates reassembled into fibrils, which were hypothesized to be composed of hydrophobic β-sheet cores and hydrophilic PEG that protruded to increase the solubility. The entanglement, crystallinity, and cross-linking of these fibrils were assumed to create a physical network that constituted the hydrogel matrix.

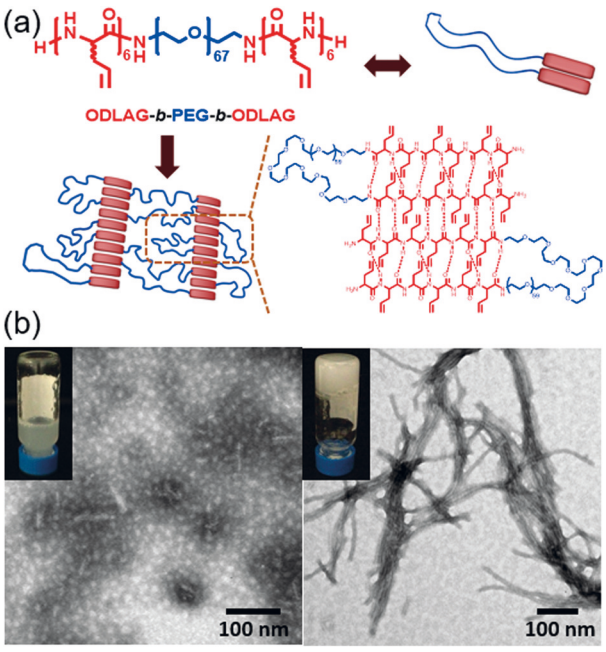


Figure 4. a) Molecular structure of ODLAG-*b*-PEG-*b*-ODLAG, a graphic illustration of the supramolecularly assembled nanostructure, and an illustration of the formation of β-sheets on the molecular scale. b) TEM images of nanostructural morphologies derived from sol and gel states. Adapted from ref. [33d] with permission from The Royal Society of Chemistry.

To further understand the effect of control over the structure of the thermoreversed gelators related to β-sheet formation, detailed studies on the relationship between the chemical compositions and gelation behavior were conducted. For example, to tune the value of T_{gel}, synthetic approaches including control of the block length,[33b] modification of the chain end groups,[40] and changes to the hydrophobic alkyl-side-chain length were investigated.[41]

Apart from β-sheet-rich systems, heat-induced gelation was also described in polypeptide gelators that adopted considerable amounts of α-helical conformation. Recently, the group of Deming designed a coil-helical structure, in which the coil was made of highly water-soluble racemic polypeptide, and the helix was derived from helicogenic polypeptides that contained poly(γ-[2-(2-methoxyethoxy)ethyl]-L-glutamate) (E^{P2}).[42] The thermoresponsive gelation phenomenon may be attributed to the lower critical solution temperature (LCST) behavior of the E^{P2} domains, of which the peptide side chains were functionalized with oligo(ethylene glycol) (OEG).[43] In addition, other α-helix-rich thermoreversed gelators were also reported; the responsive gelation driving forces were related to the dehydration of poloxamer[44] and T_{gel} was tunable through coordination of metals.[45]

In addition to hydrogelation, thermoreversed organogelation was also reported by the group of Jeong for a PEG-*block*-polypeptide copolymer in chloroform.[33e] At low temperature, this polymer assembled into micelles, which might aggregate upon increasing the temperature, resulting in organogelation of the system. Organogelation owing to intermicellar aggregation was attributed to the decreased hydrodynamic radius of PEG, which was characterized by the measurement of intrinsic viscosity.

4.1.2. Mechanical Force

Sonication typically refers to a process by which ultrasound waves are applied to generate cavitation (formation, growth, oscillation, and collapse of bubbles) in a pressure field.[46] Since 2005, there have been extensive studies on the sol–gel transitions of soft matter when ultrasound is applied.[47] Nevertheless, most of the existing sonication-induced sol–gel transition studies were based on the self-assembly and reorganization of small molecules, whereas polymeric systems were less explored.[48]

Recently, we described sonication-triggered gel-to-gel transitions in the cases of α-helix-rich organogel systems, whereas gel-to-sol transitions were observed in β-sheet-rich systems.[49] For the PEG-*block*-statistical polypeptides that had a higher α-helical content, immediate reassembly of short nanorods with maintenance of long-range interactions, in situ after sonication, facilitated the rebuilding of three-dimensional networks and resulted in sonication-triggered gel-to-gel transitions (Figure 5). On the other hand, in similar systems with higher β-sheet content, the longer nanofibrils were expressly converted into short

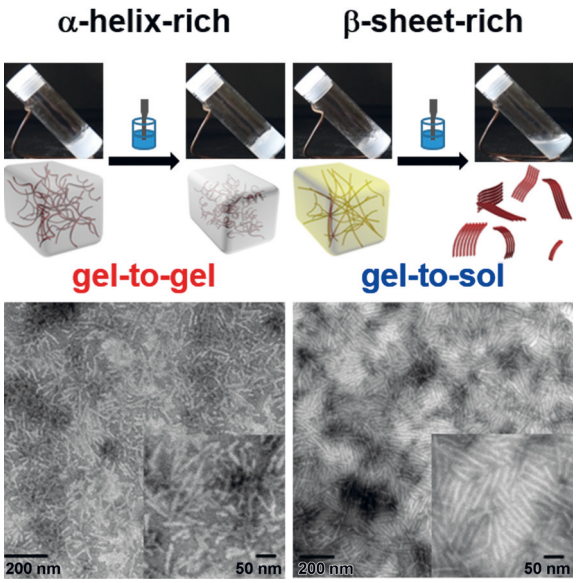


Figure 5. Schematic illustrations and TEM images of sonication-triggered gel-to-gel and gel-to-sol transitions from α-helix- and β-sheet-rich polypeptides, respectively. Adapted from ref. [49] with permission from The Royal Society of Chemistry.

nanorods, which were well aligned in nanodomains, but lacked longer range connectivity between clusters, ultimately resulting in gel-to-sol transitions.

Another sonication-triggered gel-to-sol transition system, which consisted of β-sheet-rich ODALG-*b*-PEG-*b*-ODLAG gelator, was also reported by us.[29d,33d,50] Disruption of nanofibrils with long-range interactions into discrete spherical aggregates was observed when sonication was applied, which ultimately resulted in a gel-to-sol transition (Figure 4). Based on these two studies, the effect on the external sonication-responsive property owing to secondary structural control of polypeptide-based gels provides a novel and facile method to modify the properties of stimuli-responsive materials by tuning the self-assembled nano- or microstructures without the need for precise control at the molecular level.

4.1.3. Enzyme

Owing to the presence of enzyme-cleavable amide bonds linking the amino acid repeat units along the backbone, polypeptide-based hydrogels have exhibited responsive degradation when treated with enzymes. The degradation of polypeptide hydrogels was studied both in vitro and in vivo to investigate potential applications, such as enzyme-controlled release of encapsulated cargoes, desert-greening, and agricultural materials.[33d,44,51]

In these studies, the hydrogel degradation profile was dependent on the structure of the peptide units and the type of enzymes chosen because polypeptides showed various susceptibilities towards an enzyme and enzymes also showed different efficiencies in degrading a polypeptide chain. For example, the group of Jeong reported an enzymatically degradable temperature-sensitive polypeptide, PEG-*block*-poly(alanine-*co*-phenylalanine) (PEG-PAF), of which the sol underwent gelation in situ upon injection.[51] The gel was comparably stable in phosphate buffered saline (PBS), whereas it degraded much faster in the subcutaneous layer of rats. The degradation was assumed to occur in the presence of proteolytic enzymes and was confirmed by gel permeation chromatography. In this study, various enzymes were tested and different degradation rates were observed. Another example of an enzyme-triggered gel-to-sol transition was described by us.[33d] In this study, the enzyme responsiveness of the hydrogel system was observed by studying in vitro hydrogel weight-loss profiles. Through comparison of the rate of weight loss, the efficiencies of different enzymes on triggering gel-to-sol transitions of the hydrogels were able to be compared. In addition, Yamamoto and co-workers observed the suppression of hydrolysis and breakdown of the gel matrix by incorporating unnatural amino acids into the polypeptide backbone, when the hydrogels were incubated with proteases or microorganisms that secreted hydrolytic enzymes.[52] The observation of these phenomena is fortunate because it allows optimization of the degradation profile through synthetic approaches. Unfortunately, however, enzymatic cleavage of the backbone has, to date, resulted in irreversible gel-to-sol transitions. It is worth considering how to reverse this process, perhaps by the reconstruction of a polypeptide backbone or release of a gelator from a sol-state polypeptide-based copolymer system.

There have been some interesting recent studies related to the enzyme-triggered sol-to-gel transition, with the addition of enzymes to interact with the peptide side-chain functionalities and, for instance, facilitate covalent cross-linking reactions.[53] Some of these studies are highlighted in the redox part Section 4.2.3.

4.2. General Responsive Behavior Owing to the Versatility of Polypeptide Side-Chain Functionalities

The technique to achieve responsive sol–gel transition behavior through control of the chemistries of the polypeptide side chains is not unique to polypeptide gelators, but is usually generally applicable. This technique includes the incorporation of photo-, pH-, or redox-responsive groups that undergo cross-linking or de-cross-linking upon treatment with a stimulus to achieve phase transition. In this regard, some examples are described briefly to demonstrate the versatility of polypeptides in the incorporation of various smart functional units.

4.2.1. Light

Sol–gel transitions have been extensively investigated through the chemistry of photo-cross-linking, photo-polymerization, photodegradation, or isomerization of photoactive compounds because light is one of the most convenient stimuli to manipulate, with spatiotemporal control. Previously, most peptide-based photoresponsive sol–gel transition systems were derived from oligo- or polypeptides with defined sequences.[54] To incorporate photoresponsive behavior into the polypeptides synthesized by NCA ROP, Ohkawa et al. functionalized poly(L-

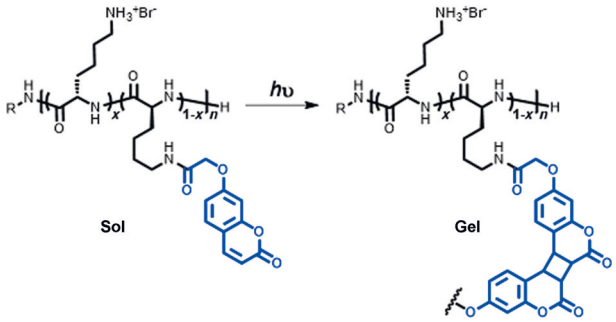


Figure 6. Chemical cross-linking through the photoinduced cyclodimerization of coumarin moieties. Adapted from ref. [54b]. Copyright 1999 American Chemical Society.

lysine) and poly(L-ornithine) side chains with coumarin moieties (Figure 6).[55] The attached coumarin underwent photoinduced cyclodimerization to create a cross-linked network, resulting in a sol-to-gel transition after light irradiation. The cross-linking densities could be controlled by light irradiation and the resulting photo-cross-linked gels were degradable by certain enzymes and microorganisms.

4.2.2. pH

Sol–gel transition systems that respond to pH changes have certain advantages over other stimulus-responsive systems. For example, in the application of injectable hydrogels, the sol state of thermoreversed gelators tends to be thickened and may experience pregelation issues, whereas pH-responsive systems were designed so that gelation would not occur until the pH of the sol was changed and approached that of physiological conditions.[56] One pH-responsive system was described by the group of Dong in 2010 (Figure 7).[57] In this system, poly(L-glutamic acid)-*block*-PEG (PLG-*b*-PEG) was dissolved in water to form normal (with PLG as the core and PEG as the shell) or reverse micelles (with β-cyclodextrin/PEG poly-pseudorotaxanes as the core and anionic PLG as the shell, with the initial addition of α-CDs and NaOH). Both the normal and reverse micelle systems displayed a pH-responsive behavior, in which gelation occurred at lower pH values when hydrogen-bonding interactions among PLG segments facilitated the formation of the hydrogel network. On the other hand, an increase in pH deprotonated the PLG segments and resulting repulsive anionic polyelectrolytes dissociated the hydrogen bonds and disrupted micellar formation, which further resulted in the gel-to-sol transition (Figure 7). In addition to sol–gel phase transitions, other macroscopic changes, such as volume phase transitions, were also achieved with polypeptide-based gels, through control of repulsive polyelectrolyte formation.[58]

4.2.3. Redox

Redox-responsive sol–gel transitions have been realized through various chemistries, such as switching the redox states of metal ions in metal complexes[59] and controlling the formation/cleavage of disulfide bonds.[60] Recently, the group

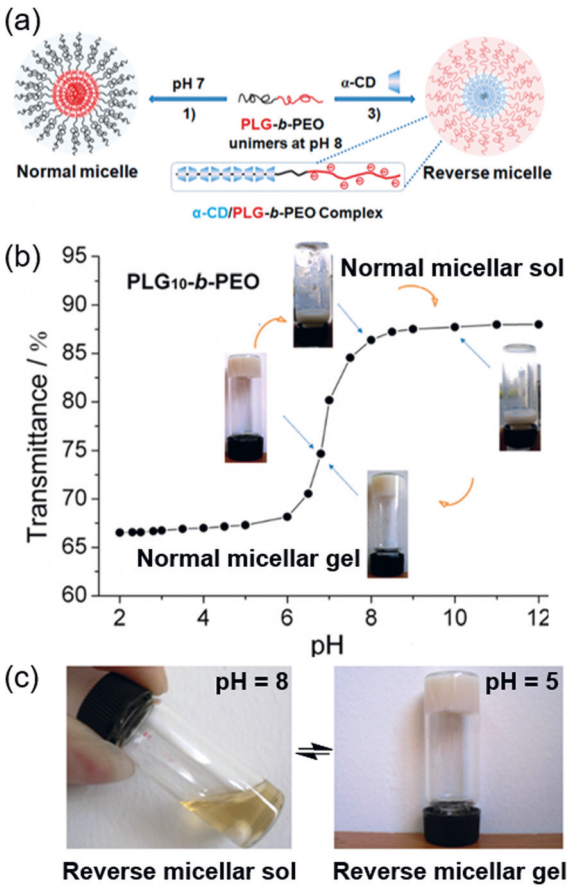


Figure 7. a) Supramolecular assembly of PLG-*b*-PEG into normal micelles and reverse micelles. α-CD = α-cyclodextrin. b) The transmittance of copolymer normal micellar solution dependence on pH (curves), which demonstrates that the sol–gel transition is pH sensitive and reversible. c) Photographs of the reverse micellar sol–gel transition in response to pH changes. Adapted from ref. [56]. Copyright 2010 Wiley-VCH.

of Chen developed an injectable hydrogel system, in which the sol-to-gel transition occurred under physiological conditions with the presence of horseradish peroxidase (HRP) and H_2O_2.[53b] The gelator (PLG-*g*-TA/PEG) was based on PLG grafted with PEG and tyramine (TA), which underwent cross-linking through enzyme-mediated oxidative reactions with HRP and H_2O_2 (Figure 8). As one of the most popular enzymes for enzymatically cross-linked hydrogels, HRP was shown to be capable of catalyzing the oxidative coupling of aniline or phenol derivatives in the presence of H_2O_2 under physiological conditions. Cross-linking of the polypeptide side-chain functionalities ultimately resulted in the formation of a hydrogel matrix that displayed a sol-to-gel transition on a macroscale. In addition, the gelation time, mechanical strength, and porous structure of the resulting hydrogel could be controlled through modulation of the HRP activity.

5. Summary and Outlook

Throughout this review, recent advances in the optimization of synthetic strategies, the study of gelation mechanisms, and the investigation of stimuli-responsive macroscopic sol–gel transi-

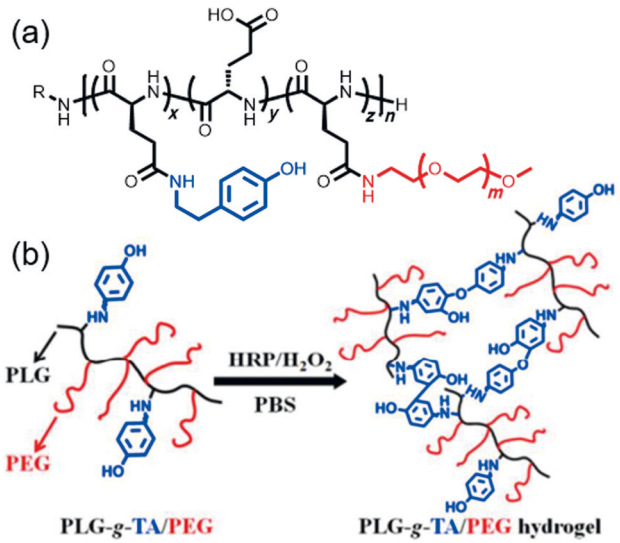


Figure 8. a) Chemical structure of PLG-*g*-TA/PEG. b) Schematic route to enzyme-mediated cross-linking of the PLG-*g*-TA/PEG copolymer. Adapted from ref. [53b] with permission from The Royal Society of Chemistry.

tions of polypeptides and peptide hybrid polymeric materials have been highlighted. Modification of experimental techniques and reaction conditions, in combination with the development of novel catalyst/initiator systems, have enabled NCA ROP to emerge as a facile and economically affordable synthetic approach toward well-defined polypeptides with desired molecular architectures, and have established a solid foundation for polypeptide-based materials with high-performance characteristics for use in mechanical, environmental, and biomedical applications. The versatility and functionality of polypeptides, which can be designed to take advantage of supramolecular hierarchical assembly processes of the peptide segments together with incorporation of a variety of stimuli-responsive properties that are available from natural and synthetic amino acid building blocks, are often unobtainable from non-polypeptide materials. The relationships between chemical compositions, supramolecular structures, and physical properties, as revealed by studies on stimuli-triggered sol–gel phase transitions, have provided guidance for the rational design of polypeptide gels with responsive properties. Despite these promising perspectives, there are still challenges for research into smart polypeptide gel materials, including the syntheses of novel NCA (or other) monomers with higher stability during production, purification, and storage through green chemistry concepts; the preparation of peptide hybrid polymeric materials through highly efficient orthogonal chemistries with other natural/synthetic biomacromolecules toward biomedical applications; the construction of more complex hierarchically assembled structures to take advantage of ordered secondary structures of polypeptides; the expansion of applications for stimuli-responsive polypeptide organo- and hydrogel systems by incorporation of functional species, including therapeutic and catalytic agents; and control of the application-appropriate physical and mechanical properties, together with the sol–gel transition rate and its reversibility. With continued research effort toward these challenges, fundamentally and practically, polypeptide-based chemistry and materials will be expected to cover wider applications and play more significant roles in smart functional materials.

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