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Heterotypic Supramolecular Hydrogels

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Abstract

Supramolecular hydrogels, formed via intermolecular interactions in water, are emerging as a new type of versatile soft materials to be applied in many areas, such as biomedical applications, catalysis, food additives, and cosmetics. While most of the supramolecular hydrogels are homotypic (i.e., one type of building blocks), heterotypic supramolecular hydrogels are less explored, but may offer unique advantages. This review describes supramolecular hydrogels that consist of more than one type building blocks (i.e., heterotypic) to illustrate the promises and challenges of heterotypic supramolecular hydrogels as soft biomaterials. First, we discuss the driving force for producing heterotypic supramolecular hydrogels. Second, we introduce the general methods for triggering heterotypic supramolecular hydrogels. Third, we summarize the examples of heterotypic supramolecular hydrogels made of hydrogelators with or without containing amino acid residues. Fourth, we describe the applications of heterotypic supramolecular hydrogels up-to-date. Finally, we give the outlook and propose a few future directions that likely worth to be explored.

1. Introduction

Supramolecular hydrogel is a soft material that consists of large amount of water as the liquid phase and a dynamic three-dimensional network formed by small molecules via non-covalent interactions as the solid phase. Being referred as hydrogelators, the small molecules self-assemble in water to form the viscoelastic 3-D network to hold water, which results in a colloidal soft material. Drive by non-covalent interactions (e.g., hydrogen bonding, Van der Waals interactions, and charge interactions) in water, supramolecular hydrogels share some common properties with extracellular matrix (ECM)¹ of cells, and are emerging as a new type of versatile biomaterials to be applied in many areas, such as tissue engineering^{2, 3}, drug delivery^{4, 5}, wound healing⁶, catalysis^{7, 8}, and control of cell fate^{9–12}.

Because of their similarities to ECM and many promising applications, supramolecular hydrogels have received increasing attentions. There are several excellent reviews that have covered most of works on supramolecular hydrogels^{12–24}. However, most reviews on supramolecular hydrogels focus on the progress of homotypic hydrogels resulting from self-assembly of single component hydrogelators, and the advance of heterotypic hydrogels containing two or more component hydrogelators has received little attentions.^{25–29} Unlike homotypic hydrogels, heterotypic hydrogels, containing two or more components

hydrogelators, confer several advantages: i) relative easiness of the synthesis of each component, especially it is easy to make ligands and receptors separately; ii) changing one of the components can easily tune the properties of the hydrogels; iii) more importantly, it is easy to produce multifunctional soft matters for sophisticated applications. Thus, it is worthwhile to summarize the development of heterotypic hydrogels for exploring new frontiers of supramolecular hydrogels. This review is arranged in the following order: we discuss the fundamental driving forces that generate heterotypical hydrogels, including using several representative examples to illustrate the non-covalent interactions. Then, we introduce the general methods for creating heterotypic hydrogels. Following that, we present the recent progresses of the heterotypical hydrogels according to their categories. Because peptide-based heterotypical hydrogels are uniquely suitable for biomedical applications, we classify the heterotypic hydrogels to two types: non-peptidic hydrogels (e.g., formed by using melamine^{30–40}) and peptide-based heterotypical hydrogels. Next, we describe several examples of the potential applications of heterotypical hydrogels. Finally, we discuss the challenge and perspective on heterotypical hydrogels. We hope that this review not only serves as an updated reference, but also can stimulate the research progresses on heterotypical hydrogels.

2. Driving force

Like homotypic supramolecular hydrogels, heterotypic supramolecular hydrogels also are resulted from non-covalent interactions (e.g., hydrogen bonding, hydrophobic interactions, and charge interactions). While each component of the heterotypic hydrogels by itself is unable to form hydrogels due to insufficient intermolecular interactions in water, the combination of different components results in new complexes via adequate non-covalent interactions. Generally, more than one type of physical interactions coexist between the different hydrogelators, such as the presence of hydrogen bonding and hydrophobic interactions,^{31–33, 37, 40–47} or the coexistence of hydrogen bonding and electrostatic interactions,^{48–51} or the presence of hydrogen bonding, hydrophobic interactions, and electrostatic interactions.^{52, 53} In general, more stable hydrogels form when multiple kinds of non-covalent interactions enhance each other in water. In this section, we arrange these driving forces according to the following classifications: i) hydrogen bonding; ii) hydrophobic (or Van der Waals) interactions; iii) electrostatic interactions; and iv) ligand-receptor interactions.

2.1 Hydrogen bonding

When hydrogen bonding is the major driving force for the self-assembly, it is common that heterotypic hydrogels are resulted from the formation of microcrystalline mixture in water. Wang et al. reported that, by changing the molar ratio of two isomeric building units (4-oxo-4-(2-pyridinylamino) butanoic acid (**1**, Scheme 1) and 4-oxo-4-(3-pyridinylamino) butanoic acid (**2**) from 7:1 to 1:3, they have obtained a series of supramolecular hydrogels that mainly rely on hydrogen bonds as the driving forces of self-assembly.⁵⁴ Tang et al. obtained single crystal of the complex of 1,2,4,5-benzene tetracarboxylic acid (BTCA) and 2-amino-3-hydroxy pyridine and found that hydrogen bonds connect the molecule to form a network.⁵⁵ In addition, Tang et al. reported that the increase of the concentrations of the

gelters (1,3,5-benzenetricarboxylic acid (**3**) and 4-hydroxypyridine (**4**) results in the corresponding increases of the diameters of the nanofibers, the density of the networks made of the nanofibers, and the amount of water immobilized in the hydrogels.⁵⁶ These observations suggest that the formation of the microcrystals of the complexes may result in the hydrogelation. Li et al. reported the heterotypic supramolecular hydrogels formed by different molar ratio of thymidine (**5**) and melamine (**6**) based on hydrogen bonding.³⁹ The hydrogels exhibit different morphologies. When the molar ratio of **5** and **6** changes from 3:1 to 1:3, the three-dimension morphologies of the matrices of the hydrogels exhibit rigid but different nanostructures, such as rods, sheets, and flowers, as revealed by scanning electron microscope (SEM) (Figure 1). Jung et al. demonstrated a two-component supramolecular hydrogel formed by the interactions of a cyanurate derivative (**7**) and 4,4-bipyridine (**8**).⁵⁷ The authors obtained a single crystal of the gel and claimed that gel formation of **7** with **8** was resulted mainly from the intermolecular hydrogen bonding between $\text{CH}\cdots\text{O}=\text{C}$ and $\text{N}\cdots\text{HOOC}$. Xu et al. recently investigated supramolecular hydrogels made of distinct nucleopeptides (**9** and **11** or **10** and **11**).⁵⁸ These nucleopeptides self-assemble to form nanofibers, which results in heterotypic supramolecular hydrogels as the consequence of intermolecular hydrogen bonding and hydrophobic interactions.

2.2 Hydrophobic or Van der Waals interactions

Anti-intuitively, hydrophobic interactions are probably the most effective and most important intermolecular interactions for forming supramolecular hydrogels. Xu et al. reported a heterotypic supramolecular hydrogel formed by the combination of two N^ε-(fluorenylmethoxycarbonyl) amino acids, NPC 15199 (Fmoc-L-Leu, **12**, Scheme 2) and N^ε-Fmoc-L-Lys (**13**).⁴⁶ Interestingly, NPC15199 was a candidate of anti-inflammatory agents. According to the fluorescent spectra, the aromatic-aromatic interactions between the fluorenyl groups provide necessary interactions for the gelation. This observation further supports the notion that aromatic-aromatic interactions enhance hydrogen bonding in water. Nilsson et al. recently reported that equal molar mixtures of Fmoc-Phe (**14**) and halogenated (F, Cl, and Br) Fmoc-Phe derivatives (**15**) rapidly co-assemble to form two-component fibrils and hydrogels.⁵⁹ Interestingly, Fmoc-Phe alone hardly self-assembles at the same conditions (in 2% DMSO/H₂O) (Figure 2). The authors found that the co-assembly is mediated by aromatic-aromatic interactions arising from a parallel intermolecular packing model in which Fmoc to Fmoc interactions and side chain to side chain interactions occur. Fan et al. demonstrated three-component supramolecular hydrogels made of amino acid derivatives (**16** or **17**), riboflavin (**18**), and melamine (**6**) via self-assembly, most likely that the driving forces are hydrogen bonds and aromatic-aromatic interactions.⁴⁰

2.3 Electrostatic interactions

The electrostatic interaction is one of the important factor for constructing the hydrogel scaffold.⁵² Since electrostatic interactions are short-range interactions, they can be an exceptionally effective contributor for hydrogelation when hydrogen bonds and hydrophobic interactions are already in place. Halder et al. mixed equal molar Fmoc-lysine (**19**, Scheme 3) and γ -amino butyric acid (**20**, an inhibitory neurotransmitter) to generate a heterotypic supramolecular hydrogel in deionized water at pH 6.4. Banerjee et al. reported that two

oppositely charged amino acids interact to generate chiral helical nanofibers as the matrices of heterotypic supramolecular hydrogels.⁶⁰ That is, the equal molar mixture of two L-isomers, Fmoc-L-glutamic acid (**21**) and L-lysine (**23**), leads to left-handed helical nanofibers (Figure 3A), whereas an equal molar mixture of two D-isomers, **22** and **24**, forms right-handed helical nanofibers (Figure 3B). In a four component racemic and equal molar mixture (**21**+**22**+**23**+**24**), both left and right-handed helical nanofibers coexist, suggesting an interesting phase separation due to chirality. Moreover, the introduction of Ca²⁺/Mg²⁺ ions disrupts the helicity of nanofibers and results in straight nanofibers in the hydrogel made of **21** and **23** (Figure 3C). The authors suggested that acid–base interaction, as a form of charge interaction, is responsible for making the helical nanofibers. Bhattacharya et al. reported that L-histidine appended pyrenyl derivative (PyHis, **25**) and phthalic acid (PA, **26**) at 1 : 1 system undergoes extensive self-assembly and results in a supramolecular hydrogel in aqueous solution.⁵³ The intermolecular hydrogen bonds, aromatic-aromatic interactions, and electrostatic interactions likely are responsible for the observed hydrogelation. According to TEM, the mixture of **25** and **26** (1: 1), at relatively low concentrations, form the vesicular nanostructures with a bilayer width about 4.2 nm. Left-handed helical fibers form upon increasing the concentration of the hydrogelators (Figure 4). The authors claimed that the intertwining of the resultant helical nanofibers eventually leads to hydrogel formation.

2.4 Ligand-receptor interactions

Usually already consisting of multiple non-covalent interactions, ligand-receptor interaction is a type of specific interactions, which involve biological events and have important applications in drug development. Xu et al. used vancomycin (**27**, Figure 5A), an antibiotic, to enhance the self-assembly of **28**, which is a receptor of vancomycin.⁶¹ Rheological experiment shows that the addition of the receptor **27** into the mechanically weak hydrogels of **28** leads to up to a ~10⁶-time increase of the storage modulus of the hydrogel. As shown in Figure 5B, **27** self-assembles to form dimer, which acts as a cross-linker to assist the hydrogelation. In a related work, Xu et al. designed a hydrogelator by using Fmoc group to replace pyrene group in **28**, which form a stable hydrogel, but the hydrogel turns into a solution after the addition of equal amount of **27**.⁶² In another case, the hydrogel of **9** and **11** (or **10** and **11**) mainly relies on the interactions between these two peptides, which also could be viewed as a type of ligand-receptor interactions.^{58, 63, 64}

3. Methods for hydrogelation

Since non-covalent interactions (e.g. hydrogen bonds, hydrophobic interactions, electrostatic interactions, ligand-receptor interactions) lead to heterotypic hydrogels, physical changes (e.g. temperature, ultrasound) or chemical changes (e.g. pH, enzyme, photochemical reactions), which can modulate non-covalent interactions, usually act as a triggering event to initiate hydrogelation. Several excellent reviews have given detailed discussions on how these changes imitate self-assembly or phase-transition, which results in supramolecular hydrogels.^{12, 13} Herein, we briefly summarize a few common methods used in the preparation of heterotypic hydrogels by describing a few recent and representative cases.

3.1 Temperature

Because hydrogen bonding and hydrophobic interaction are temperature dependent, heating-cooling becomes a common and convenient approach to generate heterotypic supramolecular hydrogels. For example, Fan et al. reported a heating-cooling method that places two-component mixture of melamine and 2-ethylhexylphosphoric acid mono-2-ethylhexyl ester in a sealed glass tube with solvent and heats the solution until the solid dissolved, and the subsequent cooling of the solution at room temperature affords a hydrogel.³⁵ Liu et al. demonstrated that precipitates or hydrogels formed depending on the molar ratios between glutamic acid based bolaamphiphile racemates and melamine when they heated and cooled the mixtures.³³ The change of the temperature probably is the most straightforward method for generating hydrogels from thermally stable heterotypic hydrogelators.

3.2 Ultrasound

As a commonly used method for dissolving or dispersing solid in a solvent, ultrasound also acts as a general method to prepare supramolecular hydrogels because it is able to break up weak interactions between the hydrogelators to form ordered and stable structures. For example, Tang et al. prepared heterotypic hydrogels by mixing 1,3,5-benzenetricarboxylic acid and 4-hydroxypyridine at their molar ratio of 1 : 2.⁶⁵ At a concentration of 1.5 wt %, after heating at 90 °C to dissolve the mixture, the authors cooled down it at 20 °C under different ultrasonic power. The authors found that higher ultrasound power results in a hydrogel with higher stability and smaller average width of the aggregating nanofibers (Figure 6). In addition, without ultrasonic treatment, the mixture is only partly gelled. Bhattacharya et al. reported two-component hydrogels of bile acids (such as lithocholic acid) and various amines (such as 1,2-ethanediamine) at a total concentration of 5.0 wt %.⁴⁸ The authors dissolved the mixture by sonicating at 60–70 °C, then cooled gradually to the room temperature to get the heterotypic hydrogels. It is common and effective for generating hydrogels by combining ultrasound and temperature change.

3.3 pH

Changing pH is another most used chemical approach to trigger self-assembly and hydrogelation. Deprotonating/protonating the acid group or basic group in the hydrogelator, pH change causes the phase-transition of hydrogelators. Meanwhile, pH also affects the intensity and strength of hydrogen bonds. For examples, Hud et al. reported a pH-responsive heterotypic hydrogel that forms upon the self-assembly of two or three monomers with two pK_a -matched recognition units (one acidic and one basic).³⁴ At pH 7, the mixture of **29** and **30** (molecular ratio is 1:1) self-assembles to form hexameric rosette structures guided by hydrogen bonds and affords a hydrogel at 0.7 wt% in total monomers (Figure 7), which can stand in the vial for more than six months. However, the hydrogel easily collapses when pH is lower than 6 or larger than 8. Meantime, **31** forms a precipitate immediately upon the addition of **29** at pH 7. To increase the lifetime of gel phase, the incorporation of **31** into the mixture of **29** and **30** can afford a hydrogel with lifetime more than 5 hours.

3.4 Others

Except the commonly used methods including temperature, pH and ultrasound described above, jet flow or light is also used to create supramolecular hydrogels. For example, Qi et al. reported a jet flow that directed self-assembly at aqueous liquid-liquid interface.⁶⁶ One is the self-assembling Fmoc-FF (**32**) bearing negative charge, and the other containing cationic polyacrylamide (CPAM). By controlling the jet flow rate, they can fabricate macroscopic sac membranes or microfibers (Figure 8). Such a facile method can generate large amount of highly ordered and functionalized materials with potential applications in drug delivery, wound dressing, and other non-biological applications. Meanwhile, light is also used to modulate the heterotypic hydrogelation. For example, Khashab et al. reported a light-responsive hydrogel composing anionic azobenzene dicarboxylate and cationic cetyltrimethylammonium bromide (CTAB), such opposite charges direct self-assembly and form self-sustainable hydrogel.⁶⁷ Since the UV-irradiation induces the cis-trans change of azobenzene, such feature can be utilized to repair the damage in the surface coating. Furthermore, this heterotypic hydrogel has potential application as a sensor for detecting the humidity environment.

4. Heterotypic supramolecular hydrogels

In this part, we review recent progresses on heterotypical supramolecular hydrogel. Because we are interested in peptide as building block of heterotypical hydrogel, we classify the heterotypic hydrogelators to two types: hydrogelators with amino acid residues and hydrogelators without amino acid residues.

4.1 Hydrogelators with amino acid residues

Peptides and amino acid-based moieties are attractive candidates for hydrogelation because the successful production of homotypic hydrogels made of peptides has stimulated numerous explorations for biomedical applications. In this section, we describe several examples on amino acid-based heterotypical hydrogels.

Yang et al. reported enzyme catalyzed dephosphorylation of **33** (Scheme 4), and the resulting amphiphilic peptide **34** self-assembles to form a stable hydrogel.⁶⁸ Notably, only 63.4% of **33** converts to the corresponding hydrogelator (**34**) when the concentration of phosphatase is 16 U/mL. According to the authors, **33** also packs in the nanofibers because of aromatic-aromatic interactions of fluorenyl groups (Figure 9). In addition, simply mixing **33** and **34** fails to afford a hydrogel and only results in a suspension. This result further demonstrates that enzyme generates **34** in a homogeneous mode. Meanwhile, Yang et al. also designed a peptide Nap-FFYGK-CA (**35**) containing cyanuric acid, which binds with melamine to form a stable complex via hydrogen bonding.³¹ Particularly, the addition of melamine with a concentration higher than 20 ppm into the solution of **35** is able to afford a stable hydrogel within 30 min. Furthermore, this method eliminates the need to extract melamine from the samples, thus such sol-gel transition provides a facile method to detect the melamine in foods and other biological samples quickly without pre-extraction processes and the need of instrument.

Xu et al. reported a simple and versatile method to prepare supramolecular hydrogel, in which they simply mix equal equiv. of N^ε-L-Fmoc-Lys (**13**) and Fmoc-L-phenylalanine (**14**), which afford a stable hydrogel (1.85 wt %) after heating-cooling cycle.⁶⁹ The resulting heterotypic hydrogel exhibits exceptional high elasticity and rapid recovery properties. Subsequently, Wang et al. reported a heterotypic hydrogel of PTZ-GFFY (**36**) and Nap-GFFY (**37**) by heating-cooling method.⁴⁷ Although each the single component could form the hydrogel, the storage moduli (5000 Pa) of the heterotypic hydrogel is at least ten times bigger than the corresponding homotypic hydrogel. Even without understanding of co-self-assembly mechanism, this work provides a simple strategy to improve the mechanical property of supramolecular hydrogels. Tanaka et al. reported that N-palmitoyl-Gly-His (PalGH, **38**) and glycerol 1-monopalmitate (GMP, **39**) co-assemble to form fibrils with twisted ribbon structures in water and result in a heterotypic supramolecular hydrogel.⁷⁰ Interesting, during the sol-gel transition by shaking, the twisted ribbon in heterotypical gel becomes sheet after 24 hours of aging, while the sheet in homotypic gel of PalGH gel hardly changes in the shaking and aging process (Figure 10). The authors suggested that the sol-gel transition is less associated with the assembled molecular configuration, but more with the change in the fibril networks. Such understanding of inter-sheet or inter-fibril interactions would be useful to design functional hydrogels.

4.2 Hydrogelators without amino acid residues

Besides the studies of the hydrogelators containing amino acid residues, considerable amounts of works have centred on the non-peptidic heterotypical hydrogel.⁷¹ For example, quite a number of studies on heterotypic hydrogel are based on melamine (**6**).^{30–40} Nandi et al. demonstrated the formation of a heterotypic hydrogel by mixing **6** and **18** in a 1 : 3 mole ratio and total concentration of 0.02 %.⁷² The authors found that the hydrogel is birefringent and thermoreversible. In addition, the hydrogel enhances photoluminescence through H-bonding. Through optical, electron, and atomic force microscopy, circular dichroism (CD) and photoluminescence (PL) spectra study, the authors suggested that gelation mechanism involves three steps: i) **6** and **18** complex formation, (ii) conformational ordering, and (iii) π - π -stacking of ordered conformers.⁴² Furthermore, the morphological properties of the heterotypical hydrogel of **6** and **18** can be easily tuned by changing the ratios. For examples, the nanotubes convert to helical nanofiber bundles when the ratios of **18** and **6** change from 1:1 to 3:1 (Figure 11).³⁷ Nandi et al. also reported three heterotypic hydrogels made by **18** with salicylic acid (**40**), dihydroxybenzoic acid (**41**), or acetoguanamine (**42**).⁴¹ The morphologies of the nanostructures of the hydrogels include bar, tape, and helical tubes for **18** with **40**, **41**, and **42**, respectively. Being compared to the two heterotypic hydrogels of **18** with **40** or **41** in equal molar, the hydrogel of **18** with **42** has the highest melting temperature, the highest critical strain, the highest shielding of protons, and the enhanced photoluminescence with a red shift. So the authors concluded that the morphology, structure, stability, and PL property of the riboflavin hydrogel depend on its complementary molecule. In addition, Nandi et al. reported that mixture of **43** with **6** also can form a stiff hydrogel in water and exhibit a pH and temperature dependent fluorescence property.⁷³ Further investigation found that the addition of certain amount of component **18** hardly affects the gelation property of **43** and **6**. Moreover, increasing the amount of **18** is able to quench the

emission of heterotypic hydrogel of **43** and **6** at 431 nm and to excite **18** to give a new emission peak (e.g., 1.25 mol% of **18** shows a peak with 555 nm).³⁸

Hud et al. demonstrated that succinate-conjugated 2,4,6-triaminopyridine (**44**) interacts with cyanuric acid (**45**) to form a rosette complex, which stacks to form long nanofibrils (> 1 μm) and results in a heterotypic hydrogel (Figure 12).⁴³ According to the authors, this work might provide insights into the origin of the first RNA-like polymer. Song et al. reported a heterotypic hydrogel by mixing di-(2-ethylhexyl)phosphoric acid (**46**) and melamine(**6**) at a 1:1 molar ratio.³⁶ FTIR and NMR spectroscopies show that hydrogen bonding acts as the main driving force to assist the mixture to form long nanofibers. The authors also found that the addition of organic solvent could tune the morphologies of the assemblies.³⁵

Tantishaiyakul and Dokmaisrijan et al. used various experimental and computational techniques to investigate the heterotypical hydrogel formed by **6** and three positional isomer of aminobenzoic acid (AB).³⁰ Based on the rheological measurement, para-aminobenzoic acid (pAB)/**6** gel is the strongest one due to the strong hydrogen bonding between **6** and pAB. It is worth to note that mAB/**6** is stronger than oAB/**6** due to existence of the zwitterionic form when the gel is heated. There are also reports of heterotypic hydrogels without using melamine. For example, Bhattacharya et al. demonstrated a facile approach to generate a heterotypic hydrogel via mixing fatty acid with oligomeric amines.⁵⁰ Specifically, stearic acid co-assembles with 3,3'-iminobis(propylamine) to form nanofibers having a width of 50–125 nm via hydrophobic interactions and salt bridge between carboxylic acid and ammonium ion. Tang et al. reported that 1,3,5-benzenetricarboxylic acid co-assembles with hydroxyl pyridine to form a stable hydrogel via hydrogen bonds and aromatic-aromatic interactions.⁴⁴ They found that the heterotypic hydrogel formed by para-hydroxyl pyridine or meta-hydroxyl pyridine exhibits excellent thermal stability, having a maximal sol-gel transition temperature of 95 °C. Meanwhile, they also demonstrated that 1,2,4-benzenetricarboxylic acid (**47**) and 4-hydroxypyridine (**48**) co-assemble to form nanofibers and result in a heterotypic hydrogel at the concentration of 5.0 wt %.⁷⁴ Notably, when the concentration is lower than the minimal gelation concentration (e.g., 2.5 wt %), the complex **47/48** forms regular spheres rather than a hydrogel (Figure 13). TEM images reveals that the spheres are composed of rod-like nanofibers. The authors suggested that such phenomenon is associated with nucleation-controlled process.

4.3 Heterotypic hydrogels guided by protein structures

Based the above discussion, heterotypic hydrogels have limited in using melamine, nucleobase interaction, or relying on serendipitous encounters of certain amino acid derivatives or peptides. It is necessary and beneficial to explore new approach for supramolecular hydrogelation based on the interactions of different molecular motifs, but with a more predictable guiding principle. In the nature, dimeric protein assemblies account for the most common form of protein assemblies.⁷⁵ The peptide sequences at the binding interface of the proteins naturally offer a reliable source or a blueprint for designing the heterotypic hydrogelators. Xu et al. choose a short pentapeptidic sequence leucine–glycine–phenylalanine–asparagine–isoleucine (LGFNI), from the binding loop of PDZ domain in synapse-associated protein 102 (SAP102), and threonine–threonine–proline–valine (TTPV) from stargazing, as a crystal structure showing that TTPV binds with LGFNI (Figure 14).⁵⁸

After connecting nucleobase to the short sequences, the authors got two pairs of heterotypic hydrogelators: thymine-KTTPV (**9**) (or adenine-KTTPV (**10**)) with thymine-LGFNI (**11**). By simple mixing of the binding nucleopeptides, the authors obtain two heterotypic hydrogels, and find that the heterodimer of nucleopeptides show excellent biostability and biocompatibility. As the first example of simply mixing two nucleopeptides to trigger supramolecular hydrogelation, this work illustrate a new and rational approach to design heterotypic hydrogel based on the crystal structures of proteins. Considering the increased numbers of protein structures available, and the interactions between proteins have become much easier to be elucidated due to the advancement of cryo-TEM, more candidates will be available for developing heterotypic supramolecular hydrogels.

The exploration of the interaction of the heterotypic hydrogelators at assembled states also provide an experimental system to study the process of dis-assembly (or dissociation) of molecular aggregates. Xu et al. connect LGFNI with NapFF,⁷⁶ a well-established motif for self-assembly. The resulting molecule, NapFFLGFI (**49**, Figure 15B), exhibits high self-assembly ability which forms a hydrogel at conditions of 622 μ M and pH= 6.4 in water. The addition of thymine-TTPV-glucosamine (**50**) to the hydrogel of molecule **49** results in gel-sol transition and promotes the proteolytic degradation of the nanofiber of **49**. To be specific, as shown in Figure 15A, after the addition of **50** into the hydrogel of **49**, the non-covalent interactions between **49** and **50** disturbs the nanofibrils of **49** and results in monomeric **49**. As the substrate of proteases (e.g., proteinase K), **49** degrades completely after the treatment of protease K at 24 h, while **50** resists proteolytic degradation by protease K. In this way, **50** can be cycled to promote the dissociation of the nanofibrils of **49**. On the contrast, the molecule without glucosamine in **50** (**51**) shows much less ability to break up the assemblies of **49** and has little impact on the proteolytic stability of the nanofibrils of **49**. This result indicated that the attachment of saccharide plays key role for accelerating the proteolytic hydrolysis of nanofibers **49**. This process, termed as supramolecular glycosylation-assisted proteolysis, indicates the unique role of saccharide in heterotypic hydrogels, which not only provides a facile approach to disrupt molecular nanofibers, but also contributes a new insight to design new molecules for treating Alzheimer disease.

5. Applications

Because of their many useful properties, such as forming hierarchical structures,⁷⁷ shear thinning,^{78, 79} self-healing,^{79–82} and exhibiting phase transition upon external stimuli,^{83, 84} supramolecular hydrogels have found numerous applications in a wide range of fields, such food processing,⁸⁵ bioanalysis,^{86, 87} drug delivery,^{81, 88} tissue engineering,⁸⁹ and biomedicine.⁷⁸ The applications of heterotypic hydrogels, however, are rather limited. Herein, we describe several examples on the applications of heterotypical hydrogels.

5.1 As the template for nanoparticle synthesis

As supramolecular hydrogels, heterotypical hydrogels exhibit order structures at nanoscale, they can act as the template for nanoparticle synthesis. For example, Bhattacharya et al. reported that stearic acid or eicosanoic acid mixes with di- or oligomeric amines to form stable gels in water. The stearic acid-amine hydrogel can serve as a medium for the synthesis

of silver nanoparticles (Ag-NP). The nanoparticles, being stabilized by the amine, adhere to the nanofibers and produce a long, ordered assembly of gel-Ag-NP composite (Figure 16). In addition, the authors found that Ag-NP synthesis in water using stearic acid or the amine alone results in immediate formation of a brownish precipitate.⁵⁰ Ballabh et al. also reported silver nanoparticle forming upon the treatment of UV in a two-component heterotypic hydrogel of maleic acid and melamine.⁴⁹ The sizes of Ag-NP attached to nanofibers are between 10 to 20 nm.

5.2 Drug release

Like homotypic hydrogels, heterotypical hydrogels possess high water content and porous structures, which allow their use for drug delivery. Qi et al. investigated vitamin B₂ encapsulation in Fmoc-FF (**32**)/CPMA hydrogel and controlled release.⁶⁶ The reported encapsulation efficiency for vitamin B₂ is 88.84 % when rhodamine B, a positive charge dye, is also incorporated into the microfibers. The authors found that the higher concentration of peptide solution during the microfiber formation results in higher rate of controlled release. Li and Fan et al. developed a heterotypical hydrogel based on riboflavin (**18**), melamine (**6**), and amino acid derivatives for controlled release of pesticides, niclosamide derivatives.⁹⁰ These components self-assemble to form a stable and robust hydrogel via hydrogen bonding and pi-pi interactions. This heterotypical hydrogel (1 mL) also is able to load 200 mg drug for sustained release up to 10 days.

5.3 A humidity sensor

Being able to response to multiple external stimuli to exhibit phase transition, heterotypical hydrogels can find applications for developing sensors. For example, Khashab et al. reported a spontaneous self-assembly of heterotypic hydrogel by mixing an anionic azobenzene dicarboxylate and a cationic surfactant cetyltrimethylammonium bromide.⁹¹ This two-component hydrogel, having a critical gelation concentration of 0.33 wt%, is able to repair damage upon UV light irradiation. The authors coated the hydrogel on gold interdigitated electrodes and tested it as a humidity sensor. They found that the sensor performs with high sensitivity and good reproducibility, due to the ability of the hydrogel to uptake water molecules.

6. Outlook

As illustrated by the heterotypic hydrogels or hydrogelators in this review, the majority of research focuses on developing heterotypic hydrogelators, which largely are resulted from serendipitous observations. In addition, most of the studies on heterotypic hydrogels concentrate on the use of melamine or nucleobase interactions to build hydrogels due to limited understanding of molecular interactions at atomic level. Meanwhile, we notice that few heterotypic hydrogel has been designed for biomedical applications, which likely are limited by the highly complex interaction between multiple components with cells. Fortunately, the advances in structural biology have revealed considerable details on the non-covalent interactions between proteins. These atomistic details revealed in the crystal structures of proteins offer a blueprint for rational design of heterotypic hydrogel.^{58, 76} On the other hand, the rapid development of technology offers new methodology to address the

challenge on molecular arrangement in heterotypic hydrogels. For example, cryo-TEM,⁹² X-ray laser,⁹³ and electron crystallography,⁹⁴ act as powerful tools to explore the atomistic details of molecular interactions. Thus, we can use the knowledge and understanding we gained to generate more functional heterotypic hydrogel to meet the need of biological applications.

Considering the complexity of biological systems, the collaboration among the scientists from different disciplines has become a prerequisite for overcoming the challenges in the biomedical applications of heterotypical hydrogels. For example, drug delivery as an important application for heterotypical hydrogels, some fundamental questions remain to be answered for the scientists. How do the drugs interact with materials? How do the complex of drug and materials enter or leave the cells? How can one track the gel materials in the body? Because the development of heterotypic hydrogels still is at its beginning, many challenges stand on the way. These challenges also point out abundant opportunities. Most importantly, the study of heterotypical hydrogels offers a feasible approach to understand and to control intermolecular interaction, which should lead to more exploration of heterotypical hydrogels in the context of cell biology. Based on this rationale, we believe the development of heterotypic supramolecular hydrogels should focus on the tunability of the hydrogels. For example, the use of biological cues to generate a hydrogel or to result in gel-sol transition. Such a kind of progress likely will lay the foundation for engineering heterotypical hydrogels as soft biomaterials for a wide range of applications. We hope this review can serve as informative reference for researchers to keep exploring the heterotypic hydrogel for creating sophisticated functional molecular biomaterials.

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Notes and references

1. Geckil H, Xu F, Zhang X, Moon S, Demirci U. *Nanomedicine*. 2010; 5:469–484. [PubMed: 20394538]
2. Silva GA, Czeisler C, Niece KL, Beniash E, Harrington DA, Kessler JA, Stupp SI. *Science*. 2004; 303:1352–1355. [PubMed: 14739465]
3. Moreira Teixeira LS, Feijen J, van Blitterswijk CA, Dijkstra PJ, Karperien M. *Biomaterials*. 2012; 33:1281–1290. [PubMed: 22118821]
4. Liang G, Yang Z, Zhang R, Li L, Fan Y, Kuang Y, Gao Y, Wang T, Lu WW, Xu B. *Langmuir*. 2009; 25:8419–8422. [PubMed: 20050040]
5. Zhang Z, He Z, Liang R, Ma Y, Huang W, Jiang R, Shi S, Chen H, Li X. *Biomacromolecules*. 2016; 17:798–807. [PubMed: 26830342]
6. Yang Z, Liang G, Ma M, Abbah AS, Lu WW, Xu B. *Chem. Commun*. 2007:843–845.
7. Rodriguez-Llansola F, Miravet JF, Escuder B. *Chem. Commun*. 2009:7303–7305.
8. Escuder B, Rodriguez-Llansola F, Miravet JF. *New J. Chem*. 2010; 34:1044–1054.
9. Shi J, Xu B. *Nano Today*. 2015; 10:615–630. [PubMed: 26900396]
10. Yang ZM, Xu KM, Guo ZF, Guo ZH, Xu B. *Adv. Mater*. 2007; 19:3152–3156.
11. Yang Z, Liang G, Xu B. *Acc. Chem. Res*. 2008; 41:315–326. [PubMed: 18205323]
12. Du X, Zhou J, Shi J, Xu B. *Chem. Rev*. 2015; 115:13165–13307. [PubMed: 26646318]
13. Estroff LA, Hamilton AD. *Chem. Rev*. 2004; 104:1201–1218. [PubMed: 15008620]

14. Zhao F, Ma ML, Xu B. Chem. Soc. Rev. 2009; 38:883–891. [PubMed: 19421568]
15. Sangeetha NM, Maitra U. Chem. Soc. Rev. 2005; 34:821–836. [PubMed: 16172672]
16. Steed JW. Chem. Commun. 2011; 47:1379–1383.
17. Ulijn RV, Bibi N, Jayawarna V, Thornton PD, Todd SJ, Mart RJ, Smith AM, Gough JE. Mater. Today. 2007; 10:40–48.
18. Suzuki M, Hanabusa K. Chem. Soc. Rev. 2009; 38:967–975. [PubMed: 19421575]
19. Branco MC, Schneider JP. Acta Biomater. 2009; 5:817–831. [PubMed: 19010748]
20. Altunbas, A., Pochan, DJ. Peptide-Based Materials. Deming, T., editor. Vol. 310. 2012. p. 135–167.
21. Fichman G, Gazit E. Acta Biomater. 2014; 10:1671–1682. [PubMed: 23958781]
22. Peppas NA, Hilt JZ, Khademhosseini A, Langer R. Adv. Mater. 2006; 18:1345–1360.
23. Ren C, Zhang J, Chen M, Yang Z. Chem. Soc. Rev. 2014; 43:7257–7266. [PubMed: 25060777]
24. Li Y, Qin M, Cao Y, Wang W. Sci. China Phys. Mech. Astron. 2014; 57:849–858.
25. Zarzar LD, Aizenberg J. Acc. Chem. Res. 2014; 47:530–539. [PubMed: 24283993]
26. Rosser J, Calvo IO, Schlager M, Purtscher M, Jenner F, Ert P. J Cell Biol. Cell Metab. 2015; 2
27. Li J, Mo L, Lu C-H, Fu T, Yang H-H, Tan W. Chem. Soc. Rev. 2016; 45:1410–1431. [PubMed: 26758955]
28. Dash J, Saha P. Org. Biomol. Chem. 2016; 14:2157–2163. [PubMed: 26786831]
29. Wang A, Shi W, Huang J, Yan Y. Soft Matter. 2016; 12:337–357. [PubMed: 26509717]
30. Tantishaiyakul V, Dokmaisrijan S, Sangfai T, Hirun N, Li L, Juntarapet S, Suknuntha K. Colloid Surf., A. 2014; 446:118–126.
31. Zhang JW, Ou CW, Shi Y, Wang L, Chen MS, Yang ZM. Chem. Commun. 2014; 50:12873–12876.
32. Dou XQ, Li P, Lu SQ, Tian XB, Tang Y, Mercer-Chalmers JD, Feng CL, Zhang D. J Mol. Liq. 2013; 180:129–134.
33. Shen Z, Wang T, Liu M. Langmuir. 2014; 30:10772–10778. [PubMed: 25136742]
34. Cafferty BJ, Avirah RR, Schuster GB, Hud NV. Chem. Sci. 2014; 5:4681–4686.
35. Niu LB, Song J, Li JJ, Tao NM, Lu M, Fan KQ. Soft Matter. 2013; 9:7780–7786.
36. Fan KQ, Niu LB, Li JJ, Feng RX, Qu R, Liu TQ, Song J. Soft Matter. 2013; 9:3057–3062.
37. Saha A, Manna S, Nandi AK. Chem. Commun. 2008:3732–3734.
38. Bairi P, Roy B, Nandi AK. Chem. Commun. 2012; 48:10850–10852.
39. Yu Z, Bai B, Wang H, Ran X, Jin G, Sun J, Zhao C, Li M. Mater. Sci. Eng. C Mater. Biol. Appl. 2011; 31:880–884.
40. Li Y, Cheng L, Liu C, Liu W, Zhu L, Fan Y, Wu Y, Li X, Zeng Q, Fan X. RCS Adv. 2015; 5:97629–97634.
41. Nandi AK, Saha A, Roy B, Esterrani A. Org. Biomol. Chem. 2011; 9:770–776. [PubMed: 21103491]
42. Saha A, Manna S, Nandi AK. Langmuir. 2007; 23:13126–13135. [PubMed: 18001072]
43. Cafferty BJ, Gallego I, Chen MC, Farley KI, Eritja R, Hud NV. J Am. Chem. Soc. 2013; 135:2447–2450. [PubMed: 23394182]
44. Tang LM, Wang YJ. Chin. Chem. Lett. 2009; 20:1259–1262.
45. Bhattacharjee S, Bhattacharya S. Chem. Asian J. 2015; 10:572–580. [PubMed: 25641826]
46. Yang Z, Gu H, Zhang Y, Wang L, Xu B. Chem. Commun. 2004:208–209.
47. Shen ZC, Wang TY, Liu MH. Chem. Commun. 2014; 50:2096–2099.
48. Pal A, Basit H, Sen S, Aswal VK, Bhattacharya S. J Mater. Chem. 2009; 19:4325–4334.
49. Yadav P, Ballabh A. Colloid Surf., A. 2012; 414:333–338.
50. Basit H, Pal A, Sen S, Bhattacharya S. Chem. Eur. J. 2008; 14:6534–6545. [PubMed: 18537217]
51. Shen JS, Cai QG, Jiang YB, Zhang HW. Chem. Commun. 2010; 46:6786–6788.
52. Halder D. Tetrahedron. 2008; 64:186–190.
53. Bhattacharjee S, Bhattacharya S. J Mater. Chem. A. 2014; 2:17889–17898.
54. Wu J, Tang L, Chen K, Yan L, Li F, Wang Y. J Colloid. Interface Sci. 2007; 307:280–287. [PubMed: 17141263]

55. Kono S, Wang Y-j, Tang L-m. Polym. Adv. Technol. 2009; 20:558–565.
56. Wang YJ, Jin X, Tang LM. Acta Polym. Sin. 2010;462–467.
57. Jung SH, Lee H, Park S, Jung JH. New J. Chem. 2012; 36:1957–1960.
58. Yuan D, Du XW, Shi JF, Zhou N, Zhou J, Xu B. Angew. Chem. Int. Edit. 2015; 54:5705–5708.
59. Ryan DM, Doran TM, Nilsson BL. Langmuir. 2011; 27:11145–11156. [PubMed: 21815693]
60. Adhikari B, Nanda J, Banerjee A. Soft Matter. 2011; 7:8913–8922.
61. Zhang Y, Yang Z, Yuan F, Gu H, Gao P, Xu B. J Am. Chem. Soc. 2004; 126:15028–15029. [PubMed: 15547990]
62. Zhang Y, Gu H, Yang Z, Xu B. J Am. Chem. Soc. 2003; 125:13680–13681. [PubMed: 14599204]
63. Shi J, Du X, Yuan D, Haburcak R, Zhou N, Xu B. Bioconjugate Chem. 2015; 26:1879–1883.
64. Shi J, Du X, Huang Y, Zhou J, Yuan D, Wu D, Zhang Y, Haburcak R, Epstein IR, Xu B. J Am. Chem. Soc. 2015; 137:26–29. [PubMed: 25522243]
65. Cao Y, Tang LM, Wang YJ, Zhang BY, Jia LK. Chem. Lett. 2008; 37:554–555.
66. Wang Y, Qi W, Huang R, Su R, He Z. RCS Adv. 2014; 4:15340–15347.
67. Samai S, Sapsanis C, Patil SP, Ezzeddine A, Moosa BA, Omran H, Emwas A-H, Salama KN, Khashab NM. Soft Matter. 2016; 12:2842–2845. [PubMed: 26908051]
68. Gao J, Wang H, Wang L, Wang J, Kong D, Yang Z. J Am. Chem. Soc. 2009; 131:11286–11287. [PubMed: 19630424]
69. Yang Z, Wang L, Wang J, Gao P, Xu B. J Mater. Chem. 2010; 20:2128–2132.
70. Matsumoto K, Shundo A, Ohno M, Saruhashi K, Miyachi N, Tsuruzoe N, Tanaka K. Phys. Chem. Chem. Phys. 2015; 17:26724–26730. [PubMed: 26394927]
71. Wei J, Wang H, Zhu M, Ding D, Li D, Yin Z, Wang L, Yang Z. Nanoscale. 2013; 5:9902–9907. [PubMed: 23982346]
72. Manna S, Saha A, Nandi AK. Chem. Commun. 2006:4285–4287.
73. Roy B, Saha A, Esterrani A, Nandi AK. Soft Matter. 2010; 6:3337–3345.
74. Wang YJ, Chen K, Tang LM. Chem. Lett. 2009; 38:472–473.
75. Goodsell DS, Olson AJ. Annu. Rev. Biophys. Biomol. Struct. 2000; 29:105–153.
76. Yuan D, Shi J, Du X, Zhou N, Xu B. J Am. Chem. Soc. 2015; 137:10092–10095. [PubMed: 26237170]
77. Yamamoto K, Yokoi H, Otani A. Macromol. Symp. 2015; 358:85–94.
78. Guvendiren M, Lu HD, Burdick JA. Soft Matter. 2012; 8:260–272.
79. Highley CB, Rodell CB, Burdick JA. Adv. Mater. 2015; 27:5075–5079. [PubMed: 26177925]
80. Miyamae K, Nakahata M, Takashima Y, Harada A. Angew. Chem. Int. Ed. 2015; 54:8984–8987.
81. Pianowski ZL, Karcher J, Schneider K. Chem. Commun. 2016; 52:3143–3146.
82. Strandman S, Zhu XX. gels. 2016; 2:1–31.
83. Sun ZF, Lv FC, Cao LJ, Liu L, Zhang Y, Lu ZG. Angew. Chem. Int. Edit. 2015; 54:7944–7948.
84. Shi JF, Gao YA, Yang ZM, Xu B. Beilstein J. Org. Chem. 2011; 7:167–172. [PubMed: 21448260]
85. Brockgreitens J, Abbas A. Compr. Rev. Food Sci. Food Saf. 2016; 15:3–15.
86. Kiyonaka S, Sada K, Yoshimura I, Shinkai S, Kato N, Hamachi I. Nat. Mater. 2004; 3:58–64. [PubMed: 14661016]
87. Wang QG, Yang ZM, Zhang XQ, Xiao XD, Chang CK, Xu B. Angew. Chem. Int. Edit. 2007; 46:4285–4289.
88. Wang X, Wang C, Zhang Q, Cheng Y. Chem. Commun. 2016; 52:978–981.
89. Rosales AM, Anseth KS. Nat. Rev. Mater. 2016; 1:15012.
90. Li YB, Zhu L, Fan YL, Li YY, Cheng LX, Liu W, Li X, Fan XL. Nanomaterials. 2016; 6
91. Samai S, Sapsanis C, Patil SP, Ezzeddine A, Moosa BA, Omran H, Emwas AH, Salama KN, Khashab NM. Soft Matter. 2016; 12:2842–2845. [PubMed: 26908051]
92. Bai, X-c, McMullan, G., Scheres, SHW. Trends Biochem. Sci. 2015; 40:49–57. [PubMed: 25544475]

93. Hauptman, HA. Science of Crystal Structures: Highlights in Crystallography. Hargittai, I., Hargittai, B., editors. Springer International Publishing, Cham; 2015. p. 19-22.
94. Shi D, Nannenga BL, Iadanza MG, Gonen T. eLife. 2013; 2:e01345. [PubMed: 24252878]

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Figure 1.

Schematic illustration of thymidine (T, **5**) and melamine (M, **6**) self-assembling to form rods, sheets and flowers via hydrogen bonds at different ratios. Adapted from Ref³⁹.

Figure 2.

(A) Chemical structures of Fmoc-Phe and halogenated (F, Cl, and Br) Fmoc-Phe derivatives.

(B) Model illustrating the potential relative orientation of the Phe (blue) and F5-Phe (green) side chains in the context of co-assembled fibrils. Adapted with permission from ref⁵⁹.

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Figure 3.

(A) AFM image of the two-component hydrogel [21 + 23] showing clearly the presence of left handed helical fibers; inset shows the helicity of single fibers. (B) AFM image of the two component hydrogel [22 + 24] showing right handed helical fibers; inset shows the helicity of single fiber; (C) AFM image of aggregates obtained from [21 + 23] in the presence of Ca^{2+} ions. Adapted with permission from ref⁶⁰. Copyright 2011 Royal Society of Chemistry.

Figure 4. Self-assembly of L-histidine appended pyrenyl derivative (PyHis, **25**) and phthalic acid (PA, **26**). Adapted with permission from ref⁵³. Copyright 2014 Royal Society of Chemistry.

Figure 5.

(A).Molecular structures of ligand, vancomycin (**27**), and receptor (**28**). (B) Illustration of supramolecular arrangement of complex of **27** and **28**. Adapted with permission from ref⁶¹. Copyright 2004 American Chemical Society.

Figure 6.

SEM photographs of assembling fibers formed under different ultrasonic power of 200, 300, 400, and 500 W from left to right, respectively. Adapted with permission from ref⁶⁵.

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Figure 7.

(A) Illustration of pH mediated self-assembly and disassembly via pKa-matched molecular recognition; (B) The molecular structure of **29–31** and plausible stacked structures. Adapted with permission from ref³⁴. Copyright 2014 Royal Society of Chemistry.

Figure 8. Schematic illustration of the jet flow directed self-assembly through the combination of an Fmoc-FF solution with a CPAM solution. Adapted with permission from ref⁶⁶. Copyright 2014 Royal Society of Chemistry.

Figure 9. Schematic illustration of enzymatic conversion and proposed molecular arrangements of **33** and **34** in the nanofibers. Adapted with permission from ref⁶⁸. Copyright 2009 American Chemical Society.

Figure 10.

TEM images for (A) the homotypic gel of **38** and (B) the heterotypic gel of **38** and **39** (equal equiv.) during the shaking and aging. Adapted with permission from ref⁷⁰. Copyright 2015 Royal Society of Chemistry.

Figure 11.

Proposed mode of supramolecular complex of riboflavin (**18**) and melamine (**6**) at the ratios of 1:1 and 3:1, at which form tubes and helical bunched fibers. Adapted with permission from ref³⁷. Copyright 2008 Royal Society of Chemistry.

Figure 12. Molecular structures of succinate-conjugated 2,4,6-triaminopyridine (**44**) and cyanuric acid (**45**), a **45/46** rosette, and the proposed assemblies formed by stacking of rosettes. Adapted with permission from ref⁴³. Copyright 2013 American Chemical Society.

Figure 13.

Macroscopic sphere formed by mixture of 1,2,4-benzenetricarboxylic acid (**47**) and 4-hydroxypyridine (**48**) at 2.5 wt %. Adapted with permission from ref⁷⁴. Copyright 2009 The Chemical Society of Japan.

Figure 14.

Protein-protein interactions inspire the molecular design of complimentary nucleopeptides, which simply mix together to trigger supramolecular hydrogelation. Adapted with permission from ref⁵⁸. Copyright 2015 Wiley Online Library.

Figure 15.

(A) Illustration of supramolecular glycosylation assisted proteolysis accelerating the degradation of molecular nanofibrils via supramolecular interactions and (B) the molecular structures of the self-assembling peptide **49** and its binding partner conjugated with (**50**) or without (**51**) a saccharide. Adapted with permission from ref⁷⁶. Copyright 2015 American Chemical Society.

Figure 16.

TEM images of gel-Ag-NP composite. a) Ag-NP synthesized in stearic acid-amine hydrogel.

b) Magnified images of Ag-NP preferentially residing on the fibers. Adapted with permission from ref⁵⁰. Copyright 2008 Wiley Online Library.

Scheme 1.

Representative molecular structures of heterotypic supramolecular hydrogelators that form hydrogels via hydrogen bonding.

Scheme 2.

Representative molecular structures of heterotypic supramolecular hydrogelators formed hydrogels by hydrophobic interactions.

Scheme 3.

Representative molecular structures of heterotypic supramolecular hydrogelators formed hydrogels by electrostatic interactions.

Scheme 4.

Representative molecular structures of heterotypic supramolecular hydrogelators formed hydrogels with amino acid residues.

Scheme 5.

Representative molecular structures of heterotypic supramolecular hydrogelators formed hydrogels without amino acid residues.