Structural design of vinyl polymer hydrogels utilizing precision radical polymerization

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Abstract

Polymer hydrogels are promising materials for various applications due to their unique properties. The precise construction of networked structures is required for the development of gel materials with improved functionality. This focus review outlines the structural design of polymer gels by utilizing precision radical polymerization techniques, mainly focusing on the authors' recent research. First, the anticipated advantages of precision radical polymerization in gel synthesis are briefly explained. Then, our approach to synthesizing gels with a homogeneous network structure is described. Finally, controlling the swelling behavior of gels prepared from two types of monomers is highlighted with a focus on the regulation of the monomer sequence in the network chains.

Introduction

Polymer hydrogels consist of a three-dimensional polymer network with water molecules within the structure (Fig. 1). This structural feature gives hydrogels soft and wet characteristics by combining solid-like properties derived from the polymer chains and liquid-like properties from the water. Because of these unique properties, hydrogels have been used for years and are considered environmentally friendly materials for various applications [1–7].

Hydrogels generally possess good flexibility, low surface friction, and desirable substance retention and permeability. In addition to these advantages, various functionalities can be imparted into the gels by selecting the appropriate polymer network chains. In particular, since the volume phase transition behavior of poly(acrylamide derivative) gels was discovered by Tanaka et al. [8], hydrogels have attracted much attention as smart materials that autonomously change their properties in response to external stimuli. One representative example is the thermoresponsive poly(N-isopropylacrylamide) (PNIPAAm) gel, which reversibly swells and shrinks at

~32 °C in pure water [9–11]. Vinyl compounds, which possess a carbon–carbon double bond, such as NIPAAm, are useful precursors for gels because of their structural diversity, and vinyl polymer gels are generally synthesized by free radical polymerization of vinyl monomers in the presence of a cross-linking agent bearing two vinyl groups, such as N,N'-methylenebisacrylamide (MBAAm). This preparation method is simple and easy, and therefore vinyl hydrogels are commonly used materials. However, it is impossible to control the network structure due to the concurrent and random propagation and cross-linking reactions (Fig. 1). The spatial distribution of cross-linking points is inhomogeneous, and the network involves unreacted vinyl groups derived from the cross-linker and dangling chains that do not contribute to the network structure [12–14]. In addition, the monomer sequence is also difficult to control when two or more kinds of monomers are copolymerized to tune the gel properties. Such uncontrollable structural factors often greatly influence the gel properties. In other words, to enhance the gel function, precise control of the network structure of the hydrogels is important. Thus, we are focusing on the utilization of a precision radical polymerization technique for the design of cross-linked structures and functionalization of hydrogels based on the control of the monomer sequence along the network chains. This focus review starts with a brief description of the advantages of precision radical polymerization in gel synthesis and outlines our recent results in two main fields: the design of cross-linked structures and

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Fig. 1 Structure and uncontrollable "inhomogeneity" of divinyl-cross-linked hydrogels
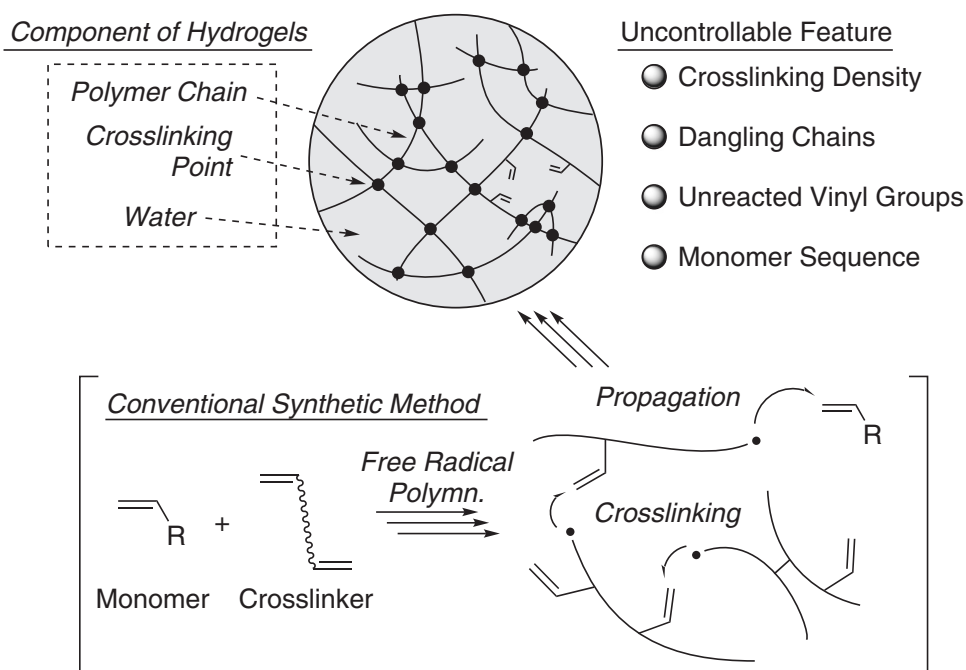
functionalization by controlling the monomer sequence in network chains.

Precision radical polymerization and sequence control in gel synthesis

Precision radical polymerization techniques have advanced remarkably in recent decades due to the development of novel catalysts and reaction mechanisms [15–21]. The important feature for controlled polymerization is the regulation of propagation reactions by reversible activation of the growing end (therefore, this method has recently been called "reversible deactivation radical polymerization"). By using such controlled polymerization, it is becoming possible to control the molecular weight and achieve narrow molecular weight distributions for various polymers. In addition, block copolymers with two or more kinds of monomers and polymers with unique topology, such as graft and star polymers, can also be obtained.

One of the advantages of using such a precision radical polymerization technique for gel synthesis is the utilization of polymers with defined structures as precursors for network formation. Here, it is also important to use a highly efficient reaction, such as "click chemistry" [22], for cross-linking to obtain the designed network. The combination of precision radical polymerization and click chemistry is a powerful tool not only for controlling the spatial distribution of cross-linking points but also for designing amphiphilic conetwork structures using block copolymers. Recent examples are discussed in the next sections.

Design of a homogeneous network

The first advantage of precision radical polymerization in gel synthesis is the design of a homogeneous network structure with a uniform molecular weight between the cross-linking points. A gel with a nonuniform network easily breaks on a macro scale due to stress concentration in network chains with low-molecular weight. Since this is directly related to the low mechanical strength of gel materials, the realization of a homogeneous network is desirable. In addition, the synthesis of a uniform network structure is considered to be the basis for the design of various gel network structures. Furthermore, obtaining such a designed network helps us theoretically understand the details of the gel properties, such as the swelling and mechanical properties. Based on these backgrounds, many studies on the synthesis of homogeneous networks have been conducted [23]. The typical synthetic method involves linking the end groups of controlled polymers with a uniform molecular weight.

One of the most successful examples in recent years is a tetra-poly(ethylene glycol) (tetra-PEG) gel reported by Sakai et al. [24]. The tetra-PEG gel is prepared by the cross reaction of two types of 4-arm star PEGs having mutually reactive terminal groups synthesized by living anionic ring-opening polymerization. These polymeric precursors have equal molecular weights with narrow molecular weight distributions and react with each other at their termini to produce highly homogeneous structures. By using this tetra-PEG gel, it is becoming possible to discuss the correlation between the theoretical and experimental physical

properties of gels in detail [25–28]. On the other hand, from the viewpoint of structural diversity, the incorporation of various functional groups into PEG-based polymers is difficult, and the preparation of a homogeneous network using various functionalized vinyl monomers is still required.

The recent development of precision radical polymerization would dramatically advance the network design of polymer gels. In particular, the combination of highly efficient reactions with a high tolerance for various functional groups is a promising approach for preparing homogeneous networks. There are two typical methods. One is the reaction of controlled telechelic polymers having reactive sites at both termini with a branched, low-molecular-weight cross-linker [29–32]. In this method, the synthesis of telechelic polymers is relatively simple using a precision radical polymerization technique, but the reaction can be affected by steric hindrance from the polymers during the cross-linking reaction. The other method utilizes four-armed star-shaped polymers as same as the synthesis of tetra-PEG gel [33–36]. For example, Oshima et al. reported the synthesis of poly(sodium acrylate) gel by this scheme [33]. They synthesized two kinds of four-branched poly(t-butyl acrylates) with azide and alkyne termini by a copper-catalyzed atom transfer radical polymerization (ATRP), and cross-linked them by a copper-catalyzed azide-alkyne cycloaddition (CuAAC) followed by deprotection of the t-butyl groups for the gel synthesis. The obtained gel showed improved mechanical properties due to its more homogeneous structure relative to that of the conventional gel prepared by divinyl cross-linking. Although this system using four-armed star polymers is promising, it requires the preparation of a branched multifunctional initiator, and more importantly, it should proceed via a uniform initiation and propagation reaction from each initiating site with maintaining its reactivity throughout the polymerization, which further complicated the reaction. In fact, in the system of Oshima et al., the polymerization was quenched in the early stage (the monomer conversion was ~20%) to avoid end-deactivation. The combination of ATRP and CuAAC is regarded as an advantageous system because both reactions proceed with the same copper catalytic system, and the polymer terminal groups obtained by ATRP are easily converted into azide groups. However, the copper catalyst should be removed after the gel synthesis prior to applications, and this purification is sometimes problematic depending on the structure of the network chains.

Thus, gel synthesis by the end-linking of controlled polymeric precursors as described above is promising for the regulation of network structures with uniform molecular weights between the cross-linking points. Furthermore, Satoh and Takeoka et al. recently reported a novel one-pot preparation method combining a multifunctional initiator

and a core-cross-linked star polymer synthesis by ATRP [37]. The exploration of such new reaction systems is also important.

Design of a homogeneous network by utilizing RAFT polymerization

Among the various precision radical polymerization techniques, we are focusing on reversible addition-fragmentation chain-transfer (RAFT) polymerization for gel synthesis. RAFT polymerization is a metal-free system using a thiocarbonylthio (-C(=S)-S-) compound called a RAFT agent, and the polymerization is controlled through rapid and reversible addition/fragmentation reactions between the growing radical chain and the polymeric RAFT agents, as shown in Fig. 2 [15–17]. This RAFT polymerization can be carried out by simply adding a RAFT agent to a conventional free radical polymerization system, and it is suitable for diverse functional monomers, including acrylamide derivatives such as NIPAAm. Furthermore, a symmetric trithiocarbonate (-SC(=S)-S-: TTC) compound can afford a telechelic polymer with a TTC group at the center of the polymer chain. Such TTC compounds can initiate RAFT polymerizations upon UV irradiation [38, 39], and Matyjaszewski et al. reported that a network polymer with built-in TTC moieties showed self-healing properties [40, 41].

Based on these features, we proposed a synthetic strategy for preparing a homogeneous network with self-healing properties to achieve excellent mechanical properties and material durability by utilizing a TTC-mediated RAFT polymerization (Fig. 3) [42]. We synthesized a telechelic PNIPAAm with succinimide ester groups, which are known as "activated esters" with high reactivity to amine compounds, at both termini by RAFT polymerization using a symmetrical TTC RAFT agent (CTA1) and end-group esterification. The obtained pre-polymer had a TTC moiety in the center of the molecule, and it was cross-linked by the reaction with a three-armed amine cross-linker. The optimization of the reaction conditions led to the successful synthesis of a chemically stable gel, but the cross-linking reaction efficiency was low, and the obtained gel was far from homogeneous. However, the obtained gels did exhibit UV-induced self-healing due to the presence of TTC groups located in the center of the network chains. These results indicated that the RAFT polymerization mechanism had a substantial impact not only in the construction of the structural components but also in the properties of the gel materials. The cross-linking efficiency requires improvement, but this strategy could facilitate the design of materials with high strength and
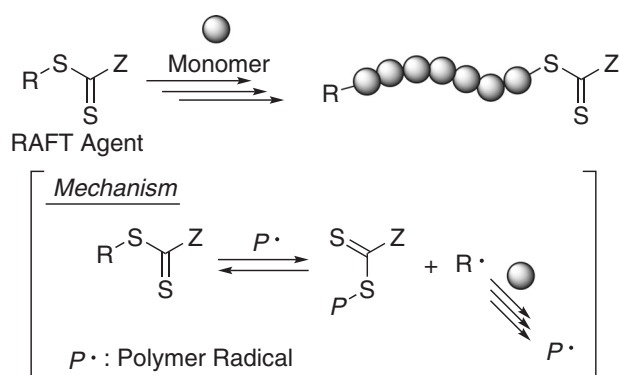
**Fig. 2** Mechanism of RAFT polymerization

durability. In particular, this end-cross-linking system using a symmetric RAFT agent can be applied to a variety of monomers because of the functional group tolerance of RAFT polymerization. This approach can afford various self-healable cross-linked polymer materials, such as hydrogels including PNIPAAm gel as well as organogels and elastomers without unique molecular features.

To improve the cross-linking efficiency in this end-cross-linking system, the appropriate selection of the cross-linking reaction and optimization of the reaction conditions are important. To this end, we then examined the thiol-ene reaction as a cross-linking reaction of telechelic polymers [43]. The thiol-ene reaction is useful for end-cross-linking systems in combination with RAFT polymerization, because this reaction is regarded as a typical click reaction with high efficiency and reactivity, and the end structure of the polymer derived from the RAFT agent can easily be converted into a thiol group by aminolysis [22, 44]. We synthesized telechelic PNIPAAm with thiol groups at both termini by RAFT polymerization using a symmetrical and bifunctional RAFT agent with two TTC groups (CTA2) followed by aminolysis (Fig. 4). Then, the gel synthesis was examined by reacting the obtained polymer with a four-armed acrylate cross-linker with azobisisobutyronitrile (AIBN) as a radical source in various solvents. The results revealed that the polarity of the reaction solvent strongly affected the molecular weight of the product, and in particular, alcoholic solvents gave stable gels. This result suggests that the expansion of the telechelic polymer in the reaction media is important in the network formation by end-cross-linking systems, which contributes to establishing design criteria for homogeneous networks. We regard controlled telechelic prepolymers prepared by RAFT polymerization as useful building blocks for the preparation of functional gel materials with homogeneous networks, and further investigations toward improving the cross-linking efficiency are being conducted.

Thermoresponsiveness expressed by copolymerization

PNIPAAm gel is a representative thermoresponsive gel that shows a reversible volume change at ~32 °C in pure water. This thermoresponsiveness is attributed to an adequate balance between hydrophilicity and hydrophobicity in the chemical structure of the monomer. The effect of the hydration of the hydrophilic amide group induces swelling of the PNIPAAm gel at low temperature, whereas increasing the temperature leads to dehydration, and simultaneously, the effect of the hydrophobic aggregation of the isopropyl group becomes dominant, causing macroscopic shrinkage of the gel (Fig. 5a). Inspired by this PNIPAAm structure with hydrophilic and hydrophobic sites coexisting in the monomeric unit, we have considered the design of thermoresponsive gels by combining a hydrophilic monomer with a hydrophobic monomer, neither of which shows thermoresponsiveness alone, to maintain an appropriate balance of hydrophilicity and hydrophobicity in the overall network. Such thermoresponsiveness achieved by combining "nonthermoresponsive" monomers has been reported in some cases for linear polymers [45–48], but to the best of our knowledge, there have been no detailed reports on such properties in polymer gels. Since thermoresponsive polymer gels showing macroscopic volume changes are considered to behave differently from linear polymers and are anticipated to have various applications, fundamental analysis and clarification of their swelling behavior is important. Furthermore, the achievement of responsiveness by combining common monomers would remarkably expand the possibilities for designing thermoresponsive materials with a variety of responsive behaviors, including the tuning of temperature and sharpness of the responsiveness, compared with what can be achieved with a gel from a single monomer.

Based on these backgrounds, we are investigating a variety of combinations of hydrophilic and hydrophobic monomers. A typical example is the copolymerization gel of hydrophilic *N,N*-dimethylacrylamide (DMAAm) and hydrophobic *N-n*-butylacrylamide (NBAAm) prepared by radical copolymerization in the presence of MBAAm [49]. This gel changed in volume in response to temperature changes as the proportion of hydrophobic monomers increased (Fig. 5b). Particularly, when the ratio of the two monomers is close to 1:1, the response behavior of the gel was relatively sharp, occurring in a small temperature range, such as that seen with PNIPAAm gel. Furthermore, when hydrophobic monomers were altered from NBAAm to isomeric monomers with different butyl groups (*iso*-butyl, *sec*-butyl, and *tert*-butyl acrylamides), the copolymerization gels with DMAAm also exhibited thermoresponsive behavior, but the behaviors were different depending on the
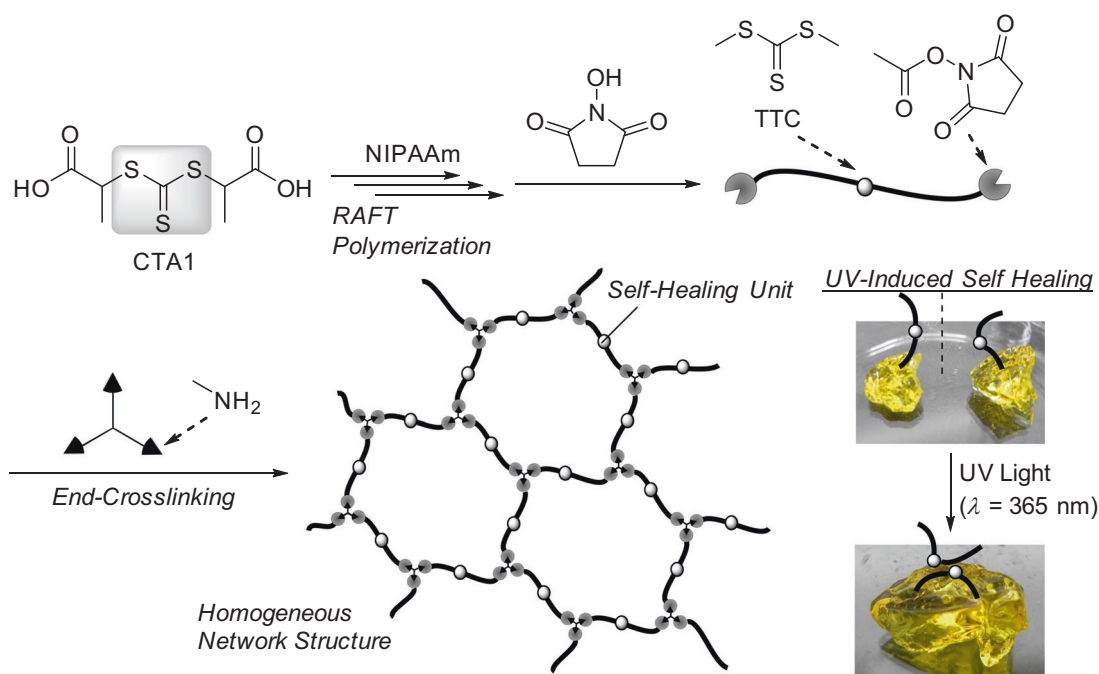
Fig. 3 Synthesis of a UV-induced self-healing homogeneous gel by the end-cross-linking of controlled telechelic prepolymers prepared via a TTC-mediated RAFT polymerization
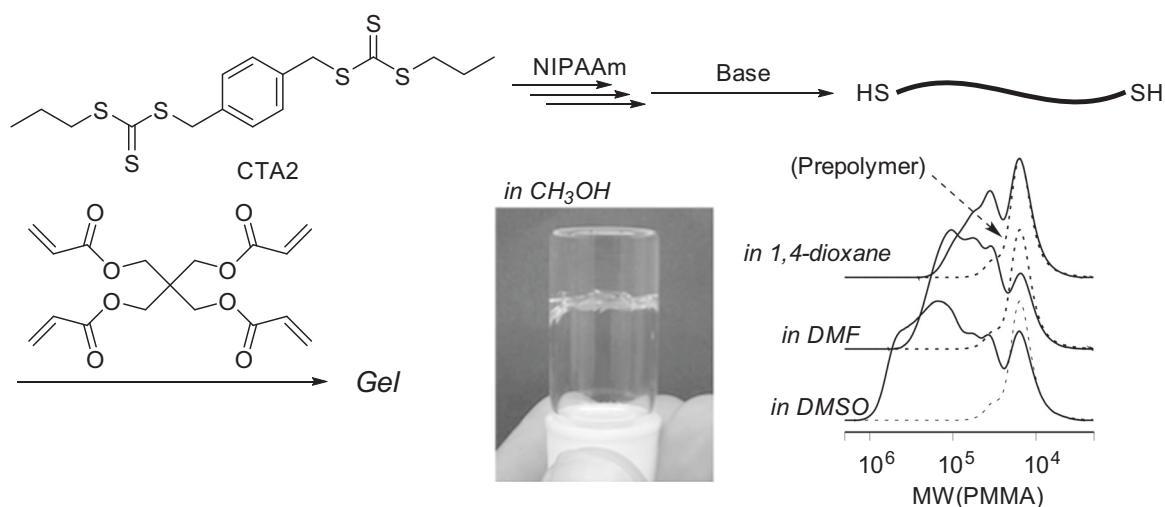

Fig. 4 Gel synthesis by the thiol-ene end-cross-linking of controlled telechelic polymers with thiol-terminals and the effect of the solvent on the reaction product

butyl structure, even at the same composition ratio. This indicates the possibility of fine-tuning of the thermo-responsive swelling behavior of polymer gels by slight structural changes to common monomers. Since the reactivities of these monomers in these combinations in the copolymerization are similar, an alternating sequence of the two monomers tends to form during the gelation reaction when the feed ratio of the monomers is close to 1:1. This hydrophilic/hydrophobic alternating structure can be regarded as a local amphiphilic structure similar to the

monomer structure of NIPAAm, which is supposed to play an important role in its thermoresponsive properties. This highlights the importance of the monomer sequence in network chains on the swelling behavior, and we are further investigating various monomer combinations to clarify the correlation between the monomer sequence and the swelling behavior of polymer gels in more detail. We also expect that the new design criteria for preparing thermoresponsive polymer gels with various responsive behaviors from a combination of common monomers could be obtained.

Fig. 5 Thermoresponsive swelling properties of polymer gels based on an appropriate hydrophilic/hydrophobic balance: **a** PNIPAAm gel and **b** P(DMAAm/NBAAm) copolymerization gel. The degree of swelling was determined from the change in the diameter of cylindrical gels, d, from the as-prepared state, d_0
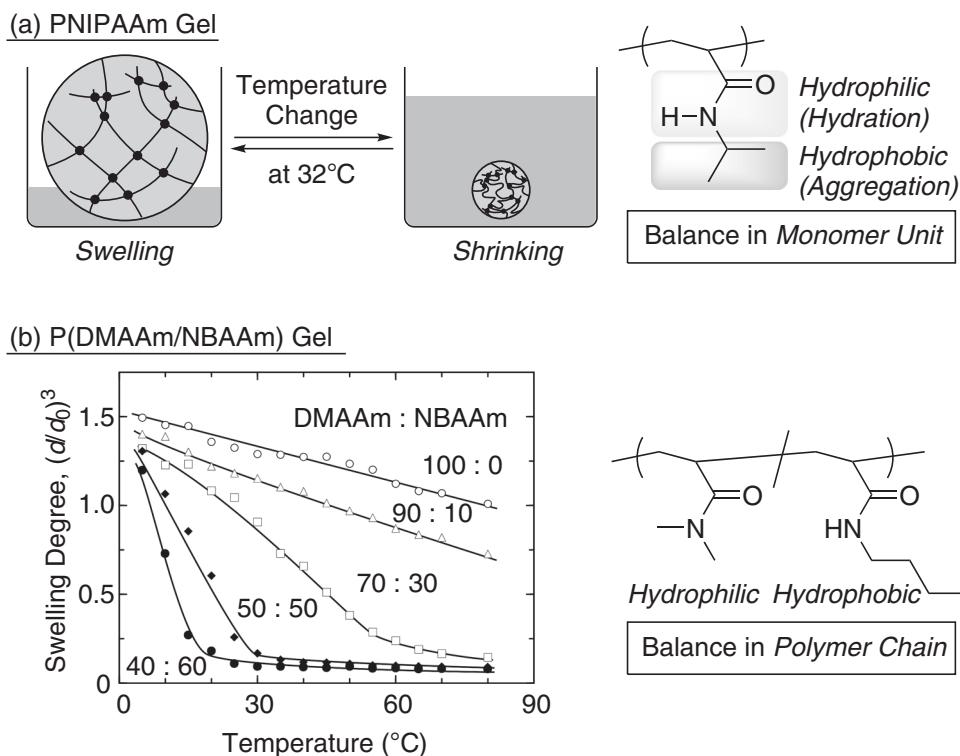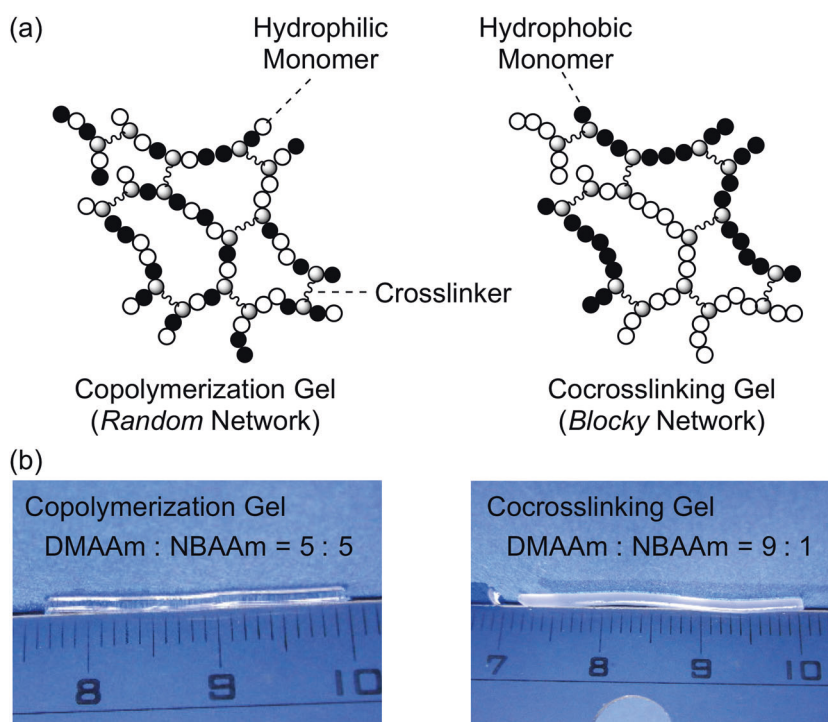

Effect of the monomer sequence in the network chains on gel properties

The properties of random copolymers and block copolymers are completely different even with the same composition. Similarly, it is necessary to consider the effect of the sequence of monomers in network chains on the properties of gels possessing two or more types of monomers even in the same composition. To this end, we expanded the aforementioned DMAAm/NBAAm combination for the construction of block-type sequence and examined the difference in swelling behavior with that of a random sequence [50]. The gels with block-type sequences were prepared by post-polymerization cross-linking of two kinds of prepolymers (PDMAAm and PNBAAm synthesized by free radical polymerization: $M_n = 44,000 \sim 54,000$; $M_w/M_n = 1.7 \sim 1.8$ determined by size-exclusion chromatography with poly(methyl methacrylate) calibration) having activated ester groups with a diamine cross-linker. We call this synthetic method "co-cross-linking" in contrast to the copolymerization method. Comparing the network structures, each network chain consists of a random sequence of the two monomers in a copolymerization gel, whereas with co-cross-linking, the gel is formed with two kinds of homopolymers, as shown in Fig. 6a. In the combination of DMAAm and NBAAm, the copolymerization gel swelled in water at low temperature even when the content of the hydrophobic component reached 50%, and it shrank as the temperature increased, as mentioned above. On the other hand, the incorporation of only 10% of

the hydrophobic component in the co-cross-linking gel resulted in shrinking and white turbidity at low temperatures, such as 5 °C (Fig. 6b).

We also investigated the effect of the monomer sequence on the thermoresponsive behavior of PNIPAAm gels combined with hydrophobic NBAAm or hydrophilic DMAAm. These copolymerized gels were also prepared by free radical copolymerizations in the presence of MBAAm, and the co-cross-linked gels were synthesized with PNIPAAm prepolymer prepared by free radical polymerization ($M_n = 77,000$; $M_w/M_n \sim 1.5$) and the aforementioned PDMAAm or PNBAAm prepolymers. As a result, the response temperature of the copolymerized gels with a random network tended to shift according to the monomer composition. That is, the incorporation of NBAAm units into the network pushed the response temperature downward, while increasing the DMAAm content resulted in a higher response temperature (Fig. 7a). In contrast, the co-cross-linked gels with block-type sequences showed only a slight change in response temperature, but the degree of swelling was strongly influenced by the monomer composition (Fig. 7b). Thus, the effect of the monomer sequence on the swelling properties of poly(acrylamide derivative) gels was clarified. Here, it should be noted that such a trend in the swelling behavior would be affected by the molecular weight of the network chains. In particular, polymer chains with lower molecular weights induce different behaviors in block-type networks even with the same composition. Now, we are trying to further elucidate the correlation between the

Fig. 6 **a** Network structure of copolymerization and co-cross-linking gels and **b** the appearance of hydrophilic/hydrophobic copolymerization and co-cross-linking gels in combinations of hydrophilic DMAAm and hydrophobic NBAAm at 5 °C

monomer sequence along the network chains and the gel properties by controlling the molecular weight of the network chains and expanding the monomer species.
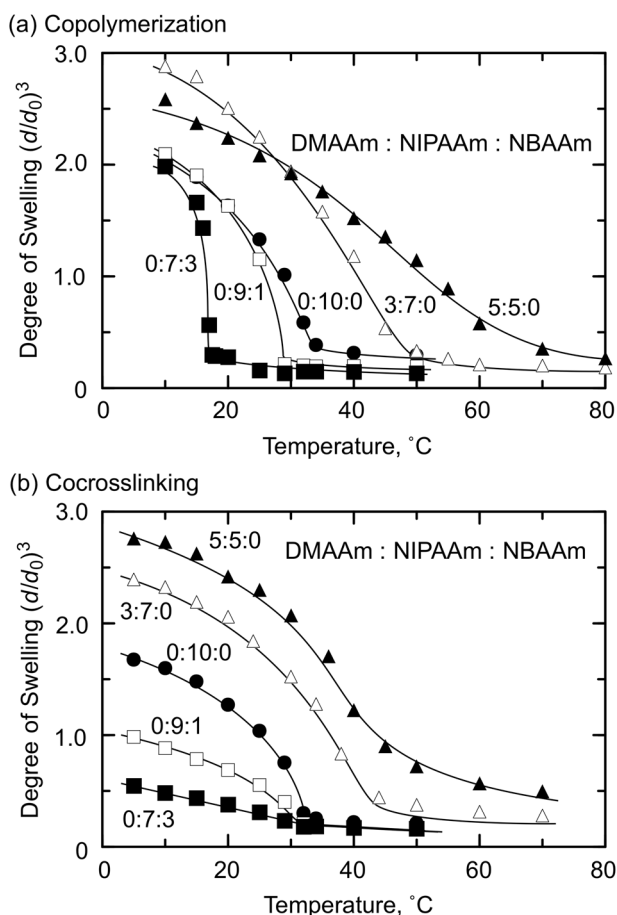
Design of cross-linked domain structures in amphiphilic conetworks

Gels composed of two kinds of polymers, such as co-cross-linked gel, are generally called amphiphilic polymer networks or amphiphilic conetworks (APCNs) [51, 52]. APCNs with appropriately designed structures show unique characteristics reflecting the properties of the two constituent polymer chains. For example, some APCNs with independent hydrophilic and hydrophobic chains are swellable both in water and organic solvents [53–58]. Stimuli-responsive chains are also attractive components for APCNs, and APCNs showing unique responses, such as rapid shrinking and mechanical toughening, have been reported [59–64].

To effectively utilize the structural features of such APCNs, the careful control of the spatial arrangement of the two kinds of polymers in the network is required. In addition to this requirement, we emphasize the importance of the spatial distribution of the cross-linking points in the APCNs because the cross-linking points are the most important feature of polymer gels departing from linear polymers. Along this line, we proposed a novel design for APCNs involving the incorporation of cross-linking points into only one part of the two polymer chains constituting the APCNs (Fig. 8) [65]. This structure consists of cross-linked

polymer domains (CDs) dispersed in the network and polymer chains bridging the CDs; therefore, the two kinds of polymer chains are distinctly compartmentalized in the network. This structural feature results in the effective incorporation of the functionalities of both polymer chains. Moreover, a polymer chain in a CD and a bridging chain differ in mobility due to the presence or absence of cross-links, which may affect the stimuli-responsive behavior depending on the sequence in the network. Such a hierarchical structure would contribute to the development of novel materials, for example sensing materials that can change stepwise in response to multiple stimuli, and a carrier holding multiple substances in different domains and changing release properties depending on the substance.

Toward the design of such APCNs, we utilized a triblock prepolymer with reactive sites only in the outer blocks. The prepolymers with inverted monomer sequences, thermoresponsive/hydrophilic/thermoresponsive and hydrophilic/thermoresponsive/hydrophilic domains, were prepared by RAFT block polymerization of NIPAAm and DMAAm using CTA2. Then, these prepolymers were cross-linked by reacting the embedded activated ester groups with a diamine crosslinker. The obtained gels are considered to form CD structures derived from the outer blocks of the triblock prepolymers. These designed gels with CD structures swelled in water at low temperatures to a much greater extent than a randomly cross-linked gel because of the CD structure, which possesses concentrated cross-linking points. In addition, these gels shrank dramatically in a narrow window in response to temperature changes due to the effective function of the
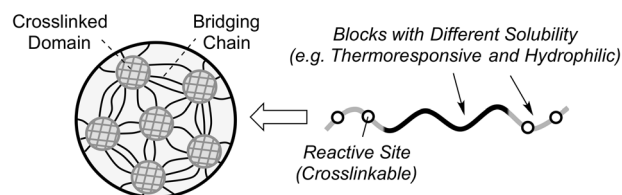
(a) Copolymerization

(b) Cocrosslinking

Fig. 7 Thermoresponsive swelling behavior of **a** copolymerized and **b** co-cross-linked gels with NIPAAm combined with DMAAm and NBAAm. The degrees of swelling were determined from the change in the diameter of cylindrical gels, d, from the as-prepared state, d_0

Fig. 8 APCN with a cross-linked domain structure synthesized from controlled triblock prepolymers with reactive sites in the outer blocks

structural complexity and the difficulties associated with their analysis. However, since polymer gels are promising materials for various applications, the precise design of network structures should not be avoided in the development of highly functional materials through the maximization of gel characteristics. The advances in precision radical polymerization have gradually opened the door to controlling the network structure and functions of polymer gels, as discussed in this focus review. We believe that gels with complicated structures are challenging and fascinating targets for synthesis and that more synthetic chemists will study the chemistry of gels in the near future. At the same time, analytical techniques have undergone remarkable advances, and further development is expected through the cooperation among researchers in diverse fields.

Compliance with ethical standards

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thermoresponsive polymer chains. Furthermore, this shrinkage is faster than that of the gel with a random monomer/cross-linker sequence because the hydrophilic domains inside the network allowed the water to efficiently exit the gel upon dehydration. Interestingly, the shrinking rate is different depending on the sequence of the triblock prepolymers, even with the same composition, probably due to the difference in the mobility of the thermoresponsive chains in CD and the bridging chains. This result suggests that the design of the triblock prepolymers, including their sequence, is the key to fine-tuning of the properties of the gel. Thus, the appropriate design of the CD structures may contribute to achieving polymer gels with novel functions, and we are further investigating not only the swelling properties but also the mechanical properties of gels with CD structures.

Summary and outlook

From the viewpoint of synthetic chemistry, polymer gels are difficult to prepare in a precise manner due to their

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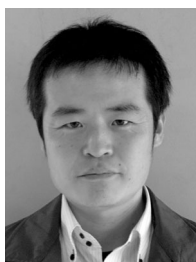
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