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The University of Osaka

# **Doctoral Dissertation**

# Studies on Mechanical Response of Functional Hydrogels Incorporating Host–Guest Inclusion Complex

ホスト-ゲスト包接錯体を組み込んだ 機能性ハイドロゲルの力学応答に関する研究

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### **General Introduction**

#### Hydrogels

Hydrogels are three-dimensional networks of cross-linked hydrophilic polymer chains with high water content<sup>1</sup>. Hydrogels have attracted much attention as they have excellent potential for applications to biomedical and biomimetic materials<sup>2-6</sup>, due to their wet and soft properties, analogous to those of living cells. Also, stimuli-responsive hydrogels are able to exhibit their functions in response to external environments, such as pH, light, ionic strength, temperature, and even specific molecules<sup>7-16</sup>, due to their high permeability derived from well-swollen networks in aqueous media. These functional hydrogels can be constructed by a well-controlled rational design of their polymer networks, and can be designed for specific purposes, such as actuators, sensors, carriers of drug delivery systems, and scaffolds of cell cultures<sup>17-20</sup>. Despite such unique features, weak mechanical properties of conventional chemically cross-linked hydrogels hinder their practical applications. Generally, hydrogels, which comprise covalent bonds acting as chemical cross-links, are fragile because applied stress readily concentrates on the covalent bonds of polymer chains and subsequential damage propagation<sup>21</sup> (**Figure 1a**). On the other hand, incorporation of non-covalent bonds acting as physical cross-links into hydrogels, such

(a) Chemically cross-linked hydrogels



**Figure 1.** Schematic illustrations of network structures of (a) chemically cross-linked hydrogels and (b) physically cross-linked hydrogels during deformation.

as hydrogen bonds, ionic bonds, coordinate bonds, hydrophobic interaction,  $\pi$ - $\pi$  stacking, and supramolecular interaction, is one of the most common and effective ways to improve the mechanical properties of the hydrogels<sup>22-28</sup>. When external force is applied to materials, the physical cross-links are cleaved sacrificially; their weak non-covalent bonds are broken instead of the covalent bonds. These cross-linking points can be reformed, reversibly and interchangeably<sup>29</sup> (**Figure 1b**), giving rise to high toughness and self-healing property of the hydrogels. Although hydrogels that merely consist of physical cross-linking points show poor mechanical strength due to inherent weak interaction of the non-covalent bonds, regulating the distribution of these bonds can greatly contribute not only to enhancement of mechanical strength, but also to the development of their functions.

#### Inclusion complexes between host and guest molecules incorporated into hydrogels

Inclusion complexation between host and guest molecules is commonly used as cross-links and functional moieties of hydrogels. Host molecules have cyclic molecular structures, and the corresponding guest molecules can be included in their cavities through host-guest interaction. In the past few decades, various kinds of host-guest complexes have been used for the construction of functional hydrogels, and the representative host units are cyclodextrins (CDs), cucurbit [n] urils, and crown ethers<sup>30-34</sup>. Appel and coworkers developed a supramolecular hydrogel cross-linked via host-guest complexation using cucurbit[8]uril, in which the formation of the hydrogel was triggered by the addition of the host molecule<sup>33</sup>. Holtz and coworkers reported sensing devices based on the host-guest interaction of crown ethers, inducing color change of the colloidal crystal hydrogels in response to metal ions<sup>34</sup>. Furthermore, Kawamura and coworkers established a breakthrough in the concept of molecular imprinting in network structures of hydrogels, using  $\beta$ -cyclodextrin ( $\beta$ -CD) as a host group<sup>15,31</sup>. In these studies, hydrogels with a controlled distribution of host molecules in their network exhibited a more significant response to a guest molecule, compared to those with random distribution of the host molecule. The host molecule distribution of the former hydrogel was regulated by the imprinting method, which uses the host-guest complex as a template during their fabrication. From these pioneer researches, it is evident that the molecular recognition abilities of host molecules towards specific guests greatly contributes to the expression of the functional characteristics of the hydrogels.

Among these attractive host molecules, CDs are widely used in the development of supramolecular hydrogels, because they have strong host–guest interaction with various organic guests. CDs are naturally derived cyclic oligosaccharides consisting of  $\alpha$ -1,4 linked glucopyranose subunits;  $\alpha$ ,  $\beta$ , and  $\gamma$ -CDs comprise 6, 7, and 8 glucopyranose units, respectively. CDs possess a relatively hydrophobic inner cavity and a hydrophilic outer surface as their hydroxyl groups are positioned facing outwards. Owing to this structure, they can form an inclusion complex with hydrophobic guest molecules with particular structures, *via* van der Waals and



Figure 2. Chemical structures of (a) β-CD and (b) Ad.(c) Schematic illustration of the inclusion complex between β-CD and Ad.



Figure 3. Schematic illustrations of (a) high elastic hydrogels and (b) self-healing hydrogels, based on host–guest complex between  $\beta$ -CD and Ad.

hydrophobic interactions, in aqueous media<sup>35</sup>. One of the most representative guest molecules for  $\beta$ -CD is adamantane (Ad), which has high hydrophobicity and a chemically stable structure (**Figure 2**). The relatively high association constant of Ad with  $\beta$ -CD created hydrogels high mechanical properties and self-healing ability, when they contained paired  $\beta$ -CD and Ad<sup>28,30,36</sup>. These hydrogels have extremely high stretchability due to the exchange of inclusion complexes, and the change in the conformation during deformation of the hydrogels, as described in the proposed mechanism reported by Kakuta and coworkers<sup>28</sup> (**Figure 3a**). Furthermore, after removing the stress, the hydrogels recovered to their original shapes, indicating that the dissociated complex reformed the initial complex. Self-healing property with high recovery ratio is also a characteristic feature of supramolecular hydrogels (**Figure 3b**). Interestingly, two freshly cut surfaces of the hydrogel adhered to each other selectively, forming a selfhealed single gel, although the freshly cut surfaces did not adhere to uncut surfaces. The authors of this report stated that when the hydrogels were cut into separate pieces, the host–guest complex, which are the weakest bonds, dissociated sacrificially. This caused the free host and guest units to be exposed at the cut surface. The host–guest complex was reformed when these surfaces were joined together<sup>36</sup>. Moreover, the physical and



Figure 4. Schematic illustrations of inclusion complexes between (a) photo-responsive azobenzene and  $\alpha$ -CD and (b) redox-responsive ferrocene and  $\beta$ -CD.

chemical properties, as well as the stability of host-guest association of the guest groups with CDs, provide specific functions to the hydrogels, such as stimuli-responsive sol-gel transition, actuation, and self-healing<sup>37-41</sup>. Specifically, *trans*-azobenzene has a larger association constant with  $\alpha$ -CD than *cis*-azobenzene with  $\alpha$ -CD, and isomerization of *trans*-azobenzene into *cis*azobenzene is induced by photoirradiation of UV light (Figure 4a). Incorporation of this photoresponsive host-guest interaction into hydrogels formed a light-driven supramolecular actuator, as reported by Takashima and coworkers<sup>39</sup>. The irradiation of UV light onto the hydrogel induced the isomerization of azobenzene, and the dissociation of the inclusion complex in the hydrogel. This led to expansion and bending of the hydrogel comparable to that of muscles, due to a decrease in the density of the cross-links in the irradiated side. On the other hand, the irradiation of visible light converted azobenzene from its *cis* to *trans* isomer, leading to reformation of the cross-links and contraction of the hydrogel, causing it to return to its original state. Wang and coworkers developed hydrogels with a reversible ion-conducting switch that can be controlled by photoirradiation. They used the difference in the association constants of  $\alpha$ -CD among guest groups: *trans* and *cis*-azobenzene, and ionic liquid motif grafted onto the hydrogel matrix<sup>42</sup>. Another representative stimuli-responsive guest is ferrocene, which exhibit redox-responsive host–guest interaction with  $\beta$ -CD. Ferrocene has a high affinity with  $\beta$ -CD in

its reduced state due to its hydrophobicity, but in its oxidized state, it has a low affinity owing to its cationic nature (**Figure 4b**). By the incorporation of this host–guest complex, the hydrogel swelled and shrunk in response to oxidation and reduction, respectively, even under high ionic strength, comparable to physiological conditions<sup>40</sup>. Additionally, the switching of self-healing ability was also controllable by redox reactions on the surface of the hydrogel<sup>41</sup>. As described above, by taking advantages of the characteristic of the guest molecules, hydrogels based on host–guest interaction between CDs and their guests are able to express functions such as high elasticity, self-healing, and stimuli-responsive properties.

#### Network design of hydrogels for high mechanical strength

As mentioned in the previous sections, enhancement of the mechanical properties of hydrogels is a critical challenge for their practical usage, in terms of life prolongation and in increasing the variety of possible applications of the material. Many strategies of network designs have been established, such as slide-ring gels, tetra-PEG gels, double network gels, and nanocomposite gels<sup>43-52</sup>. Slide-ring gels have figure-of-eight cross-linkers that can slide along the polymer chains in the network (**Figure 5a**). A typical example is the polyrotaxane gel consisting of poly(ethylene glycol) (PEG) chains and  $\alpha$ -CD rings, which are threaded on the PEG chains and trapped by capping the chain with large terminal groups, as reported by Okumura and Ito<sup>43</sup>. Sakai *et al.* developed tetra-PEG gels, which have near-ideal polymer networks, and they are prepared by the cross-end-coupling of two different tetra-functional PEG prepolymers with complementary end groups<sup>45</sup> (**Figure 5b**). By the precise control of the



**Figure 5.** Schematic drawing of network structures of (a) slide-ring gels, (b) tetra-PEG gels, (c) double network gels, and (d) nanocomposite gels.

network structures, such as polymer length between neighboring cross-links and the removal of defects and entanglements, tetra-PEG gels exhibit advanced mechanical toughness comparable to cartilage. Gong and coworkers established a novel method for obtaining strong and tough hydrogels by the fabrication of double network hydrogels via two-step network formation<sup>47</sup> (Figure 5c). The double network hydrogels are composed of a highly cross-linked, rigid and brittle first network, and a loosely cross-linked, flexible and stretchable second network. By applying stress, the first network breaks into small clusters, serving as sacrificial bonds, due to its intrinsic fragile properties, leading to the dissipation of energy and fracture propagation resistance of the second network<sup>50</sup>. Haraguchi and coworkers reported nanocomposite gels, in which most of the polymers of the matrix are grafted onto a clay nanoparticle, indicating that the nanoparticle acts as a multifunctional cross-linker<sup>51</sup> (Figure 5d). The authors suggested that the high stretchability of the nanocomposite gels arises from the relatively homogeneous distribution of cross-links, as compared to chemically cross-linked hydrogels, and the polymer chains connected to the same clay particles can sustain the force cooperatively<sup>52</sup>. As described above, to achieve hydrogels with great mechanical strength, it is essential to design their network structures with incorporation of an appropriate mechanism for energy dissipation.

On the other hand, a particle-reinforced composite is also an effective way to improve the mechanical strength of hydrogels. Composite hydrogels consist of a polymer matrix and a solid reinforcing agent with a large surface area, which acts as a filler and disperses throughout the matrix. Various kinds of reinforcing agents have been utilized to fabricate composite hydrogels, such as silica nanoparticle, montmorillonite, graphene oxide, titanate nanosheet, and cellulose nanofiber<sup>53-59</sup>. By the incorporation of these solid fillers, mechanical properties of composite hydrogels were improved, because applied stress on the matrices is transferred to the stiff reinforcing agents, leading to energy dissipation in materials. In this sense, one of the main approaches to construct composite hydrogels with excellent mechanical properties is to enhance the compatibility between the filler and the matrix. To achieve this, covalent bonds and non-covalent interactions were incorporated at the filler/matrix interfaces<sup>58-60</sup>. Kobe and coworkers reported thermoresponsive hydrogels reinforced with cellulose nanofibers, which was modified

using maleimide anhydride, to introduce a polymerizable vinyl group and an anionic charge for improved dispersibility in water<sup>59</sup>. The incorporation of covalent bonds between the filler and the matrix enabled the hydrogels to exhibit high stretchability, while retaining their thermoresponsive property. Zhong *et al.* developed self-healing composite hydrogels in which multiple cross-links of ionic interactions were incorporated among poly(acrylic acid), graphene oxide nanosheet, and Fe<sup>3+</sup> ion<sup>60</sup>. From these reports, addition of specific bonds or interaction at the filler/matrix interfaces are effective ways to improve the mechanical strength of hydrogels with functionalities.

#### **Mechanoresponsive materials**

In order to apply hydrogels in various fields, technologies to improve the safety of material usage are required. Mechano-responsive materials exhibit their functions when exposed to external stress<sup>61-63</sup>. For example, mechanochromic materials, which display an optical response in reaction to the application of a mechanical stimuli, have attracted great interest in fundamental researches and for their potential applications in stress visualization. To prevent crucial fracture of materials, the detection of damage accumulating within them is desired. Various mechano-responsive materials have been realized with varying mechanisms<sup>64-72</sup>. Incorporation of mechanophores is an impressive way to construct mechanochromic materials that utilize the mechanochemical reaction of the conversion of spiropyran to merocyanine<sup>64</sup> (**Figure 6a**). Elastomers with diarylbibenzofuranone unit in the polymer chains also exhibited mechano-



**Figure 6.** Conceptional images of mechano-responsive materials driven by (a) mechanophores, (b) photonic crystals, and (c) supramolecular assemblies.

responsive color change, induced by the dissociation of dynamic covalent bonds of the mechanophore, as reported by Imato and coworkers<sup>65</sup>. Wang *et al.* developed mechanofluorescent hydrogels functionalized by a rhodamine group<sup>66</sup>. Changes in the photonic band gap of structural color induced by the deformation of materials also take part in the mechanism of the mechano-responsive materials<sup>67-69</sup> (**Figure 6b**). Schäfer and coworkers produced elastomeric polymer films functionalized with monodisperse core-interlayer-shell polymer beads with fluorescent dyes, which change their colors in response to mechanical stress, light or temperature, reversibly<sup>67</sup>. Dynamic change in the structural form of supramolecular assemblies is also an attractive mechanism<sup>70-72</sup>. Sagara and coworkers have presented fascinating materials with rotaxanes structures as mechanochromic force transducers<sup>71</sup> (**Figure 6c**). To construct mechano-responsive materials, the transition of a driven mechanism from one state to another state, induced by mechanical force, is required.

#### Network Design of the hydrogels in this thesis

In this thesis, the author designed functional hydrogels incorporating host–guest complex between  $\beta$ -CD and Ad as sacrificial bonds in polymer networks that can dissipate energy applied to the materials (**Figure 7**). Supramolecular materials in response to mechanical force were fabricated, owing to the strong host–guest interaction of the inclusion complex in aqueous media. In chapters 1 and 2, the author developed composite materials in which the supramolecular bonding was incorporated at the interface between a filler and a matrix. The host–guest complex served as moderate physical cross-links, when the complex was formed at



**Figure 7.** Role of the host–guest interaction between  $\beta$ -CD and Ad incorporated in the hydrogels as sacrificial bonds in this thesis.

the filler/matrix interface. This enabled efficient energy transfer of applied force from the matrix to the filler, leading to the enhancement of the mechanical strength of the hydrogels. On the other hand, when hydrogels were highly deformed, the host–guest complex dissociated sacrificially, dissipating stress as energy was absorbed during this process, resulting in enhanced toughness. Moreover, in chapter 3, this host–guest interaction was utilized as a molecular switch in response to mechanical force. A certain polymer was able to maintain their metastable state when the polymer was fixed *via* the host–guest complex in the network of hydrogels. After dissociation of the complex, induced by external stress on the hydrogels, the polymer was released from the binding of the host–guest complex, and transitioned to its stable state. Mechano-responsive hydrogels were developed using the change in the different states of the polymer. As mentioned here, materials with a host–guest complex, whose formation and dissociation played different roles in response to mechanical stress, were designed.

#### **Outlines of this thesis**

In this doctoral thesis, the author presented hydrogels functionalized *via* the incorporation of host–guest interaction as sacrificial bonds in their networks. These hydrogels expressed mechanical responsive properties, such as the enhancement of strength and toughness (Chapter 1 and 2) and change in turbidity (Chapter 3). This thesis is expected to contribute to providing a platform for next-generation technologies to design hydrogels with mechanically responsive functions, as building blocks of soft materials, including biomaterials.

#### Chapter 1

In chapter 1, the author prepared a composite hydrogel, in which supramolecular bonding of an inclusion complex, formed between  $\beta$ -CD as the host molecule and Ad as the guest molecule, was introduced into a cellulose fiber/polymer matrix interface, in order to improve the mechanical strength and toughness (**Figure 8**). Ad was chemically immobilized onto the surface of the cellulose fiber. The composite gels were prepared *via* copolymerization of  $\beta$ -CD acrylamide monomer and *N*,*N*-dimethylacrylamide, in the presence of Ad-modified cellulose nanofiber. Ad-modified cellulose nanofiber acted as both the reinforcing material and the supramolecular cross-linker of the hydrogel. The mechanical strength and toughness of the composite gels were evaluated to reveal the effect of the interfacial host–guest interaction between the fiber and the matrix.



**Figure 8.** Schematic drawing of the composite hydrogel with host–guest interaction at the interface between cellulose fiber and polymer matrix.

#### Chapter 2

In chapter 2, thermoresponsive poly(*N*-isopropylacrylamide) hydrogels reinforced with supramolecular cellulose fibers were fabricated (**Figure 9**). These hydrogels change their volume in response to temperature based on its lower critical solution temperature (LCST). Ad modified cellulose nanofiber was dispersed into the thermoresponsive hydrogel matrix with  $\beta$ -CD. The thermoresponsive behavior of the composite hydrogels was evaluated. The author investigated the effect of interfacial host–guest interaction, between the filler and the matrix, on the mechanical properties of the hydrogels, both in the swelling state below the LCST and deswelling states above the LCST.



**Figure 9.** Schematic illustration of the thermoresponsive hydrogels reinforced with the supramolecular cellulose filler.

#### **Chapter 3**

In chapter 3, the author designed a mechano-responsive hydrogel that is driven by the dissociation of a host–guest complex (**Figure 10**). The hydrogel comprised thermoresponsive linear polymers, with Ad in their side chain, and a non-thermoresponsive network structure with  $\beta$ -CD. To increase the turbidity of the hydrogels by inducing phase transition under applied stress, the thermoresponsive polymer was immobilized within the hydrogel *via* host–guest interaction. Mechano-responsive change in the turbidity of the hydrogels was evaluated under various conditions to reveal the important factors. Moreover, repeatability of this mechano-responsive behavior, which is induced by temperature control based on the LCST of the thermoresponsive polymer, was investigated.



**Figure 10.** Schematic drawing of the mechano-responsive hydrogels driven by the dissociation of the host–guest complex.

#### References

- 1. T. Tanaka, Sci. Am. 1981, 244, 124.
- 2. N. A. Peppas, J. Z. Hilt, A. Khademhosseini, R. Langer, Adv. Mater. 2006, 18, 1345.
- 3. L. Ionov, Adv. Funct. Mater. 2013, 23, 4555.
- 4. P. I. Lee, J. Control. Release 1985, 2, 277.
- 5. M. Hamidi, A. Azadi, P. Rafiei, Adv. Drug Deliv. Rev. 2008, 60, 1638.
- 6. M.J. Mahoney, K. S. Anseth, Biomaterials 2006, 27, 2665.
- 7. P. Gupta, K. Vermani, S. Garg, Drug Discov. Today 2002, 7, 569.
- 8. G. Kocak, C. Tuncer, V. Bütün, Polym. Chem. 2017, 8, 144.
- 9. A. Suzuki, T. Tanaka, Nature 1990, 346, 345.
- 10. L. Li, J. M. Scheiger, P. A. Levkin, Adv. Mater. 2019, 31, 1807333.
- 11. F. Gao, Y. Zhang, Y. Li, B. Xu, Z. Cao, W. Liu, ACS Appl. Mater. Interfaces 2016, 8, 8956.
- 12. C. Qian, T Asoh, H. Uyama, Chem. Commun. 2018, 54, 11320.
- 13. Y. Hirokawa, T. Tanaka, J. Chem. Phys. 1984, 81, 6379.
- 14. Y. Kaneko, K. Sakai, A. Kikuchi, R. Yoshida, Y. Sakurai, T. Okano, *Macromolecules* **1995**, 28, 7717.
- 15. A. Kawamura, T. Kiguchi, T. Nishihata, T. Uragami, T. Miyata, *Chem. Commun.* **2014**, *50*, 11101.
- 16. T. Miyata, T. Uragami, K. Nakamae, Adv. Drug Deliv. Rev. 2002, 54, 79.
- 17. Z. Liu, P. Calvert, Adv. Mater. 2000, 12, 288.
- 18. C. Zhang, G. G. Cano, P. V. Braun, Adv. Mater. 2014, 26, 5678.
- 19. T. R. Hoare, D. S. Kohane, Polymer 2008, 49, 1993.
- S. Gerecht, J. A. Burdick, L. S. Ferreira, S. A. Townsend, R. Langer, G. Vunjak-Novakovic, Proc. Natl. Acad. Sci. U.S.A. 2007, 104, 11298.
- C. Norioka, Y. Inamoto, C. Hajime, A. Kawamura, T. Miyata, NPG Asia Mater. 2021, 13, 34.
- 22. X. Hu, M. Vatankhah-Varnoosfaderani, J. Zhou, Q. Li, S. S. Sheiko, *Adv. Mater.* 2015, 27, 6899.
- 23. X. Dai, Y. Zhang, L. Gao, T. Bai, W. Wang, Y. Cui, W. Liu, Adv. Mater. 2015, 27, 3566.
- 24. J. N. Hunt, K. E. Feldman, N. A. Lynd, J. Deek, L. M. Campos, J. M. Spruell, B. M. Hernandez, E. J. Kramer, C. J. Hawker, *Adv. Mater.* **2011**, *23*, 2327.
- 25. M. S. Menyo, C. J. Hawker, J. H. Waite, Soft Matter 2013, 9, 10314.
- 26. D. C. Tuncaboylu, M. Sari, W. Oppermann, O. Okay, Macromolecules 2011, 44, 4997.
- 27. B. Xing, C. W. Yu, K. H. Chow, P. L. Ho, D. Fu, B. Xu, J. Am. Chem. Soc. 2002, 124, 14846.
- 28. T. Kakuta, Y. Takashima, A. Harada, Macromolecules 2013, 46, 4575.
- 29. J. Cui, A. Campo, Chem. Commun. 2012, 48, 9302.
- 30. J. Park, S. Murayama, M. Osaki, H. Yamaguchi, A. Harada, G. Matsuba, Y. Takashima, Adv.

Mater. 2020, 32, 2002008.

- 31. K. Matsumoto, A. Kawamura, T. Miyata, Macromolecules 2017, 50, 2136.
- 32. G. Liu, Q. Yuan, G. Hollett, W Zhao, Y. Kang J.Wu, Polym. Chem. 2018, 9, 3436.
- 33. E. A. Appel, F. Biedermann, U. Rauwald, S. T. Jones, J. M. Zayed, O. A. Scherman, *J. Am. Chem. Soc.* **2010**, *132*, 14251.
- 34. J. H. Holts, S. A. Asher, Nature 1997, 389, 829.
- 35. M. V. Rekharsky, Y. Inoue, Chem. Rev. 1998, 98, 1875.
- T. Kakuta, Y. Takashima, M. Nakahata, M. Otsubo, H. Yamaguchi, A. Harada, *Adv Mater*. 2013, 25, 2849.
- 37. S. Tamesue, Y. Takashima, H. Yamaguchi, S. Shinkai, A. Harada, *Angew. Chem. Int. Ed.* **2010**, *49*, 7461.
- 38. H. Yamaguchi, Y. Kobayashi, R. Kobayashi, Y. Takashima, A. Hashidzume, A. Harada, *Nat. Commun.* **2012**, *3*, 603.
- 39. Y. Takashima, S. Hatanaka, M. Otsubo, M. Nakahata, T. Kakuta, A. Hashidzume, H. Yamaguchi, A. Harada, *Nat Commun.* **2012**, *3*, 1270.
- 40. M. Nakahata, Y. Takashima, A. Hashidzume, A. Harada, *Angew. Chem. Int. Ed.* **2013**, *52*, 5731.
- 41. M. Nakahata, Y. Takashima, H. Yamaguchi, A. Harada, Nat. Commun. 2011, 2, 511.
- 42. H. Wang, C. N. Zhu, H. Zeng, X. Ji, T. Xie, X. Yan, Z. L. Wu, F. Huang, *Adv. Mater.* **2019**, *31*, 1807328.
- 43. Y. Okumura, K. Ito, Adv. Mater. 2001, 13, 485.
- 44. C. Liu, N. Morimoto, L. Jiang, S. Kawahara, T. Noritomi, H. Yokoyama, K. Mayumi, K. Ito, *Science* **2021**, *372*, 1078.
- 45. T. Sakai, T. Matsunaga, Y. Yamamoto, C. Ito, R. Yoshida, S. Suzuki, N. Sasaki, M. Shibayama, U. Chung, *Macromolecules* **2008**, *41*, 5379.
- 46. M. Shibayama, X. Li, T. Sakai, Colloid Polym. Sci. 2019, 297, 1.
- 47. J.P. Gong, Y. Katsuyama, T. Kurokawa, Y. Osada, Adv. Mater. 2003, 15, 1155.
- 48. T. L. Sun, T. Kurokawa, S. Kuroda, A. B. Ihsan, T. Akasaki, K. Sato, M. A. Haque, T. Nakajima, J. P. Gong, *Nat. Mater.* **2013**, *12*, 932.
- J.Y. Sun, X. Zhao, W. R. K. Illeperuma, O.Chaudhuri, K.H. Oh, D. J. Mooney, J. J. Vlassak, Z. Suo, *Nature* 2012, 489, 133.
- 50. M. A. Haque, T. Kurokawa, J. P. Gong, Polymer 2012, 53, 1805.
- 51. K. Haraguchi, T. Takehisa Adv. Mater. 2002, 14, 1120.
- 52. K. Haraguchi, T. Takehisa, S. Fan, Macromolecules 2002, 35, 10162.
- M. Zhong, X. Y. Liu, F. K. Shi, L. Q. Zhang, X. P. Wang, A. G. Cheetham, H. Cuib, X. M. Xie, *Soft Matter* 2015, *11*, 4235.
- 54. G. Gao, G. Du, Y. Sun, J. Fu, ACS Appl. Mater. Interfaces, 2015, 7, 5029.
- 55. R. Liu, S. Liang, X. Z. Tang, D. Yan, X. Li, Z. Z. Yu, J. Mater. Chem. 2012, 22, 14160.
- 56. M. Liu, Y. Ishida, Y. Ebina, T. Sasaki, T. Hikima, M. Takata, T. Aida, Nature 2015, 517, 68.

- 57. T. Asoh, T. Yamamoto, H. Uyama, Sci. Rep. 2020, 10, 17173.
- 58. T. Zhang, T. Zuo, D. Hu, C. Chang, ACS Appl. Mater. Interfaces 2017, 9, 24230.
- 59. R. Kobe, S. Iwamoto, T. Endo, K. Yoshitani, Y. Teramoto, Polymer 2016, 97, 480.
- 60. M. Zhong, Y. T. Liu, X. M. Xie, J. Mater. Chem. B 2015, 3, 4001.
- 61. H. Izawa, K. Kawakami, M. Sumita, Y. Tateyama, J. P. Hill, K. Ariga, *J. Mater. Chem. B* **2013**, *1*, 2155.
- 62. T. Matsuda, R. Kawakami, R. Namba, T. Nakajima, J.P. Gong, Science 2019, 363, 504.
- Z. Wang, J. Wang, J. Ayarza, T. Steeves, Z. Hu, S. Manna, A. P. Esser-Kahn, *Nat. Mater.* 2021, 20, 869.
- D. A. Davis, A. Hamilton, J. Yang, L. D. Cremar, D. Van Gough, S. L. Potisek, M. T. Ong, P. V. Braun, T. J. Martínez, S. White, *Nature* 2009, 459, 68.
- 65. K. Imato, T. Kanehara, T. Ohishi, M. Nishihara, H. Yajima, M. Ito, A. Takahara, H. Otsuka, *ACS Macro Lett.* **2015**, *4*, 1307.
- 66. L. Wang, W. Zhou, Q. Tang, H. Yang, Q. Zhou, X. Zhang, Polymers 2018, 10, 994.
- 67. C. G. Schäfer, M. Gallei, J. T. Zahn, J. Engelhardt, G. P. Hellmann, M. Rehahn, *Chem. Mater.* 2013, 25, 2309.
- 68. Y. Yue, T. Kurokawa, M. A. Haque, T. Nakajima, T. Nonoyama, X. Li, I. Kajiwara, J. P. Gong, *Nat. Commun.* 2014, *5*, 4659.
- 69. G. H. Lee, T. M. Choi, B. Kim, S. H. Han, J. M. Lee, S. H. Kim, ACS Nano 2017, 11, 11350.
- 70. Y. Sagara, T. Kato, Nat. Chem. 2009, 1, 605.
- 71. Y. Sagara, M. Karman, E. Verde-Sesto, K. Matsuo, Y. Kim, N. Tamaoki, C. Weder, *J. Am. Chem. Soc.* **2018**, *140*, 1584.
- 72. C. Löwe, C. Weder, Adv. Mater. 2002, 14, 1625.

### **Chapter 1**

# Composite hydrogels incorporating a host-guest complex at the cellulose fiber/matrix interface

#### **1-1. Introduction**

Hydrogels have attracted considerable attention, and hold great potential application in the field of soft materials and biomaterials<sup>1-4</sup>, due to their wet and flexible properties. Because hydrogels are three-dimensional networks composed of cross-linked hydrophilic polymer chains with high water content, the practical applications of the conventional chemically crosslinked hydrogels are limited due to their poor mechanical properties. Therefore, to improve their mechanical properties, many strategies have been established to prepare different types of network structures<sup>5-7</sup>. Especially in nanocomposite hydrogels and particle-reinforced hydrogels, small particles with a large surface area lead to an increased interaction between the filler and the polymer matrix, enhancing the mechanical properties<sup>8-12</sup>. To construct a composite hydrogel with excellent mechanical strength, one of the key approaches is to improve the compatibility between the fillers and the matrices<sup>13</sup>. To accomplish this goal, covalent bonds and non-covalent interactions such as ionic interaction, hydrophobic interaction, and hydrogen bonding, were incorporated at the interface between fillers and matrices<sup>14-17</sup>. Among them, the host-guest interaction<sup>18</sup> consisting of CDs and their guest molecules is expected to exhibit excellent performance as supramolecular bonding of the host-guest complexes, because the supramolecular bonding will be stronger than the typical non-covalent interactions, such as hydrogen bonding and van der Waals force in water. The complexes are also less affected by ionic strength than by ionic bonding<sup>18</sup>.

CDs are well-known attractive host molecules that include various organic guest molecules in their cavities by supramolecular assembly<sup>18</sup>. The ability to form these host–guest interactions leads to CDs being applied in many fields, such as reversible adhesion, actuator, self-healing materials, drug delivery system, adsorbent materials, and catalysis<sup>19-22</sup>. Especially in the supramolecular materials including hydrogels using CDs, the materials show specific mechanical properties, such as elasticity, stretching, stress recovery, and self-healing properties

due to the reversibility of non-covalent bonding<sup>19,23</sup>. Nevertheless, the hydrogels with supramolecular functionalization between fillers and matrices utilizing host–guest interaction has rarely been reported<sup>24</sup>.

Recently, cellulose nanofibers (CNFs) derived from biomass resources have attracted significant attention. Due to the outstanding renewability, biocompatibility, ultrahigh tensile stiffness, and lower specific gravity than inorganic fillers, CNFs have been widely investigated as environmentally friendly reinforcing particles in both research and industry<sup>25-28</sup>. The surface of CNF presents numerous hydroxyl groups, which enables a wide range of chemical reaction pathways for fabrication of composite materials with useful properties<sup>29</sup>. Using pristine CNF as the raw material, the author employed a facile esterification to introduce a guest molecule for the enhancement of the compatibility between the filler and the matrix of the composite hydrogel. The CNF modified with a guest molecule acted as both the reinforcing material and the supramolecular cross-linking points in the hydrogels.

In this chapter, the author designed composite hydrogels with an enhanced interfacial compatibility through the supramolecular complex between the cellulose fiber and the matrix (CD-Ad gel, **Figure 1-1**). To improve the mechanical strength and toughness, physical crosslinking points of the inclusion complex were incorporated into the composite hydrogels.  $\beta$ -CD as a host molecule was incorporated into the matrix, and the surface of CNF was modified by Ad as a guest molecule. *In situ* copolymerization of *N*,*N*-dimethylacrylamide (DMAAm) and 6-acrylamido- $\beta$ -CD ( $\beta$ -CDAAm) in the presence of Ad-modified CNF, was selected to form the inclusion complexes efficiently in both pre-gel dispersions and hydrogels. The mechanical strength and the toughness of the fabricated hydrogels were investigated by tensile tests.



**Figure 1-1.** Schematic drawing of the composite hydrogel with host–guest interaction at the interface between cellulose fiber and polymer matrix.

#### **1-2. Experimental section**

#### **Materials and Methods**

Cellulose powder was obtained from Nacalai Tesque Inc. DMAAm, 4dimethylaminopyridine (DMAP), and N,N'-dicyclohexylcarbodiimide (DCC) were purchased from FUJIFILM Wako Pure Chemical Corporation. 1-Adamantanamine hydrochloride (Ad-NH<sub>3</sub>Cl) was purchased from Tokyo Chemical Industry Co., Ltd. Ammonium persulfate (APS) was purchased from Sigma-Aldrich. 6-Acrylamido-β-CD (β-CDAAm) was obtained from Yushiro Chemical Industry Co., Ltd. All reagents were used as purchased, without further purification. 1-Adamantanamide hexanoic acid (AdHex-COOH), and 6-amino-β-CD (β-CD- $NH_2$ ) were prepared according to the previous reports<sup>30,31</sup>.

#### Preparation of Ad-modified cellulose nanofiber (Ad-CNF)

An aqueous suspension of cellulose powder (1.5 wt%) was used for the aqueous counter collision (ACC) treatment using Star-Burst Mini (Sugino Machine Ltd., Japan), under an ejecting pressure of 230 MPa with 30 passes, resulting in an aqueous dispersion of CNF (1.5 wt%).

Ad-CNF was synthesized by a condensation reaction between a carboxylic group of AdHex-COOH and a hydroxyl group of cellulose fiber (**Figure 1-2a**). The aqueous dispersions of CNF (1.5 wt%, 15 mL) were diluted with acetone (20 mL) in 50 mL centrifuge tubes and mixed using a vortex mixer. The dispersions were centrifuged at 9000 rpm, and the supernatant was removed from the mixture. The CNF was redispersed in acetone and centrifuged to remove the supernatant. The dispersion medium was solvent-exchanged to acetone through repeated redispersion and centrifugation (five cycles). The dispersion of CNF in acetone was collected in a flask by adding acetone and homogenized by stirring. The dry content of the dispersion was determined by gravimetric analysis. The dispersion was dried in an oven (120 °C, 1 h). AdHex-COOH (1.26 g, 0.4 eq./anhydrous glucose unit, AGU) and DMAP (0.77 g, 0.6 eq./AGU) were dissolved in the CNF dispersion in acetone (244 g, 0.7 wt%). DCC (1.32 g, 0.6 eq./AGU) was dissolved in acetone (10 mL), and this solution was added to the CNF dispersion and allowed to react for 24 h at room temperature. After quenching with methanol (50 mL), the

dispersion was centrifuged at 9000 rpm to remove unreacted reagents. To remove *N*,*N*-dicyclohexylurea and other unreacted reagents from the precipitates, the dispersion medium was exchanged to methanol by repeated redispersion and centrifugation (15 cycles). Finally, the dispersion medium was solvent-exchanged to pure water by repeated redispersion and centrifugation (five cycles) to obtain an Ad-CNF aqueous dispersion. The dry content of the dispersion was determined by gravimetric analysis. Drying was performed using a lyophilization machine. The weight ratio of the dispersion was adjusted to 2.0 wt% by adding a suitable amount of pure water. The yield of the dispersion was 75 g.

#### General preparation of composite hydrogels (CD-Ad gels)

The composite hydrogels possessing supramolecular bonding were prepared by free-radical copolymerization of DMAAm and  $\beta$ -CDAAm, in the presence of Ad-CNF. The total concentration of monomers was 2.0 mmol/g<sub>mixture</sub>. DMAAm and  $\beta$ -CDAAm were dissolved in the Ad-CNF aqueous dispersion (2.0 wt%, 4.0 g). The molar ratio of  $\beta$ -CDAAm/DMAAm was 0/100, 1/99, 3/97, 5/95 (Ad, CD1-Ad, CD3-Ad, CD5-Ad gels, respectively). APS ( $8.0 \times 10^{-2}$  mmol) as an initiator was dissolved in the dispersion, and the degassing was performed by using a diaphragm pump. The degassed solution was poured on an assembly of glass and silicon elastomer spacer mold. The polymerization was performed at 50 °C for 6 h. The prepared hydrogels were immersed in water for 2 days. The water was exchanged several times for the removal of unreacted monomer and initiator.

#### Preparation of composite hydrogels using CNF as a filler (CD-CNF gels)

To perform control experiments, composite hydrogels without supramolecular bonding were prepared by free-radical copolymerization of DMAAm and  $\beta$ -CDAAm, in the presence of the CNF. The total concentration of monomers was 2.0 mmol/g<sub>mixture</sub>. DMAAm and  $\beta$ -CDAAm were dissolved in the CNF aqueous dispersion (1.5 wt%, 4.0 g). The molar ratio of  $\beta$ -CDAAm/DMAAm was 0/100, 1/99, 3/97, 5/95 (CNF, CD1-CNF, CD3-CNF, CD5-CNF gels, respectively). APS (8.0 × 10<sup>-2</sup> mmol) as an initiator was dissolved in the dispersion, and the degassing was performed by using a diaphragm pump. The process for molding, polymerization,

and removal of unreacted monomers and initiator from hydrogels, was the same as the one followed in the previous section.

#### Preparation of composite hydrogels in the presence of inhibitors

To carry out an inhibition test, the composite hydrogels were prepared by the copolymerization of the monomers in the presence of  $\beta$ -CD-NH<sub>2</sub> as the competitor of the supramolecular bonding between the filler and the matrix.  $\beta$ -CD-NH<sub>2</sub> (182 mg, 0.17 mmol) was dissolved in the pre-gel dispersion mixture of the CD1-Ad gel (CD1-Ad +  $\beta$ -CD-NH<sub>2</sub> gel). Other conditions were the same as the preparation of the CD-Ad gels.

#### Measurements

Attenuated total reflection Fourier transform infrared (ATR-FT-IR) spectroscopy (Thermo Scientific Nicolet iS 5, USA) was used to confirm the successful preparation of Ad-CNF. The samples were dried using a vacuum freeze-drier before FT-IR analysis. Elemental analysis was carried out to determine % content of carbon (C), hydrogen (H) and nitrogen (N). The analyses were measured using JM 10 (J-Science Lab Co., Ltd., Japan). Scanning electron microscopic (SEM) analysis was carried out with a Hitachi SU3500 microscope (Hitachi High-Tech Corporation, Japan). The viscosity of the dispersion mixtures was measured using Hakke Rheostress 6000 (Thermo Scientific, USA) equipped with a cone-plane measuring cell (diameter 35 mm, cone angle 1°), at a shearing speed of 1000 s<sup>-1</sup> and a temperature of 20 °C. The weight percentage of Ad-CNF in aqueous dispersions was adjusted to 1.0 wt%.  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD were added to them in amounts of 10 mg/g<sub>mixture</sub>. Mechanical properties of the gels were measured by tensile tests using a tensile tester (Shimadzu EZ-Graph) in an ambient atmosphere. The tensile test was performed at 10 mm/min in tensile mode. The tensile measurements were performed using six test pieces for each sample to evaluate the mechanical properties. The toughness of the hydrogels was calculated by integrating the area up to the tensile elongation at the maximum stress of the stress-strain curves. For the stepwise loading and unloading measurement, the tensile test was performed at 10 mm/min. A single sample was stretched to the strain at 20, 40, 60, 80, 100, 120 and 140%, in this order. The hydrogel was unloaded immediately after reaching to the certain strain in each cycle. The stress and strain in loading step were recorded.

#### 1-3. Results and Discussion

#### **Characterization of Ad-CNF**

**Figure 1-2b** shows the FT-IR spectra for AdHex-COOH, unmodified CNF, and Ad-CNF. In the spectra of both CNF and Ad-CNF, two major absorption bands at 3000–3600 cm<sup>-1</sup> and 2800–3000 cm<sup>-1</sup> were observed, which are derived from the OH and the CH stretching vibrations, respectively. In the Ad-CNF spectrum, the bands at 1740 cm<sup>-1</sup> and 1640 cm<sup>-1</sup> were



**Figure 1-2.** (a) Modification of CNF with Ad group. (b) FTIR spectra of AdHex-COOH, CNF, and Ad-CNF. SEM images of (c) CNF and (d) Ad-CNF.

assigned to the C=O stretching vibrations of the incorporated Ad unit (Ad-CONH(CH<sub>2</sub>)<sub>5</sub>COOR and Ad-CONH(CH<sub>2</sub>)<sub>5</sub>COOR, respectively; R stands for cellulose). The band at 1540 cm<sup>-1</sup> was related to the amide II vibration of Ad-CNF and AdHex-COOH.

In the spectrum of AdHex-COOH, the strong bands at 3400 cm<sup>-1</sup>, 2800–3000 cm<sup>-1</sup>, 1720 cm<sup>-1</sup>, and 1600 cm<sup>-1</sup> are said to be due to the OH, CH stretching, and the C=O stretching vibrations of carboxyl and amide groups, respectively. The results from the FT-IR spectra attested to the successful modification of the CNF surface with Ad group by the condensation reaction. The degree of substitution values of Ad-CNF calculated from C/N ratio in elemental analysis was 0.089. The fiber of CNF and Ad-CNF surface was observed by scanning electron microscopy (**Figure 1-2c,d**). In the case of CNF, the width of the fiber was 0.5–2.5  $\mu$ m and the length was 10–50  $\mu$ m, approximately. On the other hand, in the case of Ad-CNF, fibers were not able to be observed, forming large particles. From these results, the aggregation of Ad-CNF through the reaction was marked.

#### **Dispersibility of Ad-CNF**

The Ad-CNF aqueous dispersion showed а lower viscosity than the CNF aqueous dispersion, because the fibers are aggregated due the to hydrophobic interaction among Ad groups on the surface of the Ad-CNF in water. The viscosity of the Ad-CNF aqueous dispersion increased when  $\beta$ -CD was added to the dispersion (Figure 1-3a). The visual observation of the dispersions revealed enhanced an



**Figure 1-3.** (a) Viscosity of Ad-CNF aqueous dispersions (black line) with  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD (blue, red, and green line, respectively). (b) Image of Ad-CNF aqueous dispersion with and without  $\beta$ -CD. (c) Illustration of the formation of the host–guest complex on the surface of Ad-CNF.

dispersibility of Ad-CNF by the addition of  $\beta$ -CD (**Figure 1-3b**), suggesting that the hydrophilicity of the surface of Ad-CNF was improved by covering the hydrophobic Ad group with hydrophilic  $\beta$ -CD (**Figure 1-3c**). Moreover, no significant difference was found in the viscosity when  $\alpha$ -CD and  $\gamma$ -CD were added. It is known that the host–guest interaction of  $\alpha$ -CD and  $\gamma$ -CD with Ad is considerably weaker than the interaction of  $\beta$ -CD with Ad. Thus, this result demonstrates the molecular recognition ability of  $\beta$ -CD with Ad group.

#### Mechanical properties of composite hydrogels

For fabrication of the composite hydrogels, DMAAm and  $\beta$ -CDAAm were copolymerized in the presence of Ad-CNF. By addition of  $\beta$ -CDAAm to the Ad-CNF dispersion, the dispersibility of Ad-CNF was enhanced. Also, as shown in **Figure 1-4c**, the appearance of the CD-Ad gels was translucent due to the good dispersibility of the filler. This indicates that  $\beta$ -CDAAm with high mobility in an aqueous solvent was able to form inclusion complexes with Ad on the surface of the filler effectively by host–guest interaction in the pre-gel dispersion, leading to high dispersibility of the filler in the hydrogels (**Figure 1-4a**). The mechanical properties of CD-Ad gels, which have supramolecular bonding at the interface between Ad-CNF and the matrix, were evaluated by the stress–strain curves of the tensile tests, as shown in **Figure 1-5a**. The maximum stress of CD-Ad gels drastically increased with increasing molar ratio of the in-feed  $\beta$ -CDAAm, and its maximum value was  $60 \pm 3$  kPa for the CD5-Ad gel. Further, the Young's modulus of the composite hydrogel increased from 8 to 40 kPa with increase in the concentration of  $\beta$ -CDAAm from 0 to 5.0 mol% (**Table 1-1**). In Addition, water content of CD-Ad gels decreased as increasing the amount of  $\beta$ -CD in the matrices. Thus, the strength of CD-Ad gels is proportionate to the content of the host molecule in the matrix,



**Figure 1-4.** (a) Schematic illustration for the preparation of CD-Ad gels. Chemical structures of (b)  $\beta$ -CDAAm. (c) Photograph of the composite hydrogel (CD5-Ad gel).

required to form physical cross-linking points at the filler/matrix interface. This enhancement in the mechanical properties is attributed to two factors. First, in the case of a higher concentration of  $\beta$ -CDAAm in the pre-gel dispersion mixture, a larger number of the inclusion complexes existed on the surface of Ad-CNF. In consequence, a larger amount of physical cross-linking points was more efficiently incorporated into the hydrogels, leading to a drastic increase in the maximum stress of the CD-Ad gels. In other words, the improvement of the compatibility of the filler/matrix interface resulted in the enhancement of the strength of the hydrogels. Second, Ad-CNF had a larger surface area at higher  $\beta$ -CDAAm concentration, due to the greater filler dispersibility in the presence of  $\beta$ -CD (Figure 1-3). Thus, the great interfacial compatibility between Ad-CNF and the matrix was obtained by the increasing the filler surface area via host-guest complexation. Due to this, the higher  $\beta$ -CD content with a high dispersibility of Ad-CNF lead to significant improvement in the mechanical strength of CD-Ad gels. Thus, the maximum stress and Young's modulus of CD-Ad gels increased with increasing  $\beta$ -CD content in the matrix. The concentration of  $\beta$ -CDAAm in-feed is 2.0 × 10<sup>-2</sup>,  $6.0 \times 10^{-2}$ ,  $10 \times 10^{-2}$  mmol/g<sub>mixture</sub>, in CD1-Ad, CD3-Ad, CD5-Ad gels, respectively. On the other hand, the concentration of Ad group on the surface of Ad-CNF in the pre-gel dispersion mixture, is approximately  $1 \times 10^{-2}$  mmol/g<sub>mixture</sub>.

<b>Table 1-1.</b> Water content, maximum stress ( $\sigma$ ), elongation at maximum stress ( $\epsilon$ ), Young's modulus ( $E$ ),	and
toughness of CD-Ad gels.	

Samples W	Water content	σ	3	Ε	Toughness
	%	kPa	%	kPa	kJ m <sup>-3</sup>
Ad	97	$16 \pm 2$	$167\pm9$	$8\pm0.5$	$13 \pm 2$
CD1-Ad	95	$37\pm2$	$160\pm7$	$16\pm2$	$29\pm3$
CD3-Ad	93	$55\pm2$	$134\pm8$	$29\pm1$	$38\pm 3$
CD5-Ad	92	$60\pm3$	$101\pm 8$	$40\pm3$	$31\pm5$

Even though the number of the host molecule is more than that of the guest molecule, the larger amount of the incorporated  $\beta$ -CD in the matrix resulted in the enhancement of the maximum stress of CD-Ad gels. This is because not all Ad groups were incorporated into the cavity of βCD in the composite hydrogels. However, a larger number of the host–guest complexes was formed at a high concentration of  $\beta$ -CD. As a result, the compatibility between filler/matrix and the dispersibility of filler in matrix improved at higher content of  $\beta$ -CD in the polymer matrix. In this manner, once again, the mechanical strength and Young's modulus of CD-Ad gels increased by increasing the amount of  $\beta$ -CD.

To clarify the effect of the host–guest interaction, the stress–strain curves of the composite hydrogels utilizing unmodified CNF as a filler, shown in **Figure 1-5b**, revealed that no significant improvement was observed in the maximum stress of the CNF-reinforced hydrogels. Although, the elongation decreases and the maximum breaking strength increases as the amount of CD introduced increases, this is considered to be simply because the solid content in the gel increased. Taking into the account this control experiment, incorporation of the interfacial host–guest interaction utilizing Ad-CNF is effective for improving the mechanical strength of the composite hydrogels.



**Figure 1-5.** Stress–strain curves of (a) CD-Ad and (b) CD-CNF gels, and (c) their toughness.

Toughness of materials is also important in the evaluation of mechanical properties. The toughness of CD-Ad gels determined from the stress–strain curves is shown in **Figure 1-5c**. The toughness was also enhanced at the higher molar ratio of  $\beta$ -CDAAm. It showed maximum value in the CD3-Ad gel with a value of  $38 \pm 3$  kJ m<sup>-3</sup>. The supramolecular bonding involves the enhancement of the compatibility between the filler and the matrix. It effectively acted as physical cross-linking points of CD-Ad gels. Furthermore, the cleavage of the reversible bonding also dissipated mechanical energy sacrificially when the hydrogels were deformed. The toughness of CD5-Ad gel is slightly lower than that of CD3-Ad gel as the elongation of CD5-Ad is the lowest. The stress–strain curves of CD-CNF gels imply that the maximum strain of the hydrogels depends on the copolymer composition of the matrix. Consequently, the maximum strain of CD-Ad gels also decreased with an increase in the in-feed molar ratio of  $\beta$ -CDAAm. In contrast to this behavior of the CD-Ad gels, no significant improvement of toughness was observed at the higher  $\beta$ -CDAAm content in the control experiments where unmodified CNF was used as the filler of the composite hydrogels (**Figure 1-5c**).

The results of the stepwise loading and unloading measurement on CD3-Ad gel are shown in **Figure 1-6**. The stress in each cycle increased below that of the previous cycle with increasing elongation rate, and reached the original stress value when the elongation rate exceeded that of the previous cycle. This suggests that the sacrificial dissociation of the host–guest complex was promoted when the hydrogels were highly stretched, contributing to the enhancement of their toughness<sup>32</sup>.



**Figure 1-6.** Stress–strain curves of a single sample of CD3-Ad gel in stepwise loading and unloading measurement.

The importance of introducing supramolecular bonding at the filler/matrix interface in the polymerization process was demonstrated by the synthesis of composite gels in the presence of  $\beta$ -CD-NH<sub>2</sub> as the competitive inhibitor. As shown in **Figure 1-7a**, fabrication of CD1-Ad gel in the presence of  $\beta$ -CD-NH<sub>2</sub> leads to an obvious decrease in the tensile strength. This result

revealed that the competitive host molecules inhibited the formation of the supramolecular bonding between the filler and the matrix (**Figure 1-7b**). Therefore, it is noted that the enhancement of the mechanical strength and toughness of CD-Ad gels was due to the incorporated supramolecular bonding at the filler/matrix interface.



**Figure 1-7.** (a) Stress–strain curves of CD1-Ad and CD1-Ad with  $\beta$ -CD-NH<sub>2</sub> gels. (b) Schematic illustration for CD-Ad gel in the presence of the host competitor.

The proposed mechanism for the enhancement of the mechanical properties of CD-Ad gels is described below (**Figure 1-8**). The host–guest complex on the surface of Ad-CNF served as multi-point physical cross-links when the complex was formed at the filler/matrix interface. This enabled efficient energy transfer of applied force from the matrix to the filler when the hydrogels were stretched. This led to the enhancement of both the maximum stress and Young's modulus of the hydrogels. On the other hand, when hydrogels were highly deformed, the host–



Figure 1-8. Schematic drawing of the network of the hydrogels under tensile stress.

guest complex dissociated sacrificially, absorbing energy. This led to stress dissipation in the material. Moreover, owing to this, the network of the matrix was able to be stretched further, reducing stress concentration. As a result, the toughness of the hydrogels was improved significantly.

To confirm the effect of polymer matrix concentration, the fabrication of CD-Ad gels at a low in-feed monomer concentration of 1.0 mmol/g<sub>mixture</sub> was performed. The previous hydrogels shown in **Figure 1-5** were fabricated at a concentration of 2.0 mmol/g<sub>mixture</sub>. **Figure 1-9a** revealed that the toughness of CD-Ad gel increased even at a low concentration of the polymer matrix. In general, the mechanical property of hydrogels decreases at a low polymer concentration because of less entanglement of polymer chains. Moreover, total interaction between the filler and the matrix will be relatively weaker at the lower concentration of the matrix. However, the toughness of CD-Ad gels with 1.0 mmol/g<sub>mixture</sub> monomer concentration was enhanced by increasing  $\beta$ -CD content in the matrix, and the value of toughness is close to the value for the gels fabricated at the concentration of 2.0 mmol/g<sub>mixture</sub>. This is because the host–guest complex between  $\beta$ -CDAAm and Ad was efficiently formed on the surface of Ad-CNF in the pre-gel dispersions in advance before polymerization. As a result, the toughness of the hydrogels was improved since the filler/matrix compatibility improved steadily even for low polymer concentration.

Furthermore, CD-Ad gels composed of different polymer matrix were fabricated by using acrylamide and 2-hydroxyethyl acrylate as monomers. The toughness of these gels increased at



**Figure 1-9.** Toughness of CD-Ad gels composed of (a) PDMAAm, (b) poly(acrylamide), and (c) poly(2-hydroxyethyl acrylate). The gels were prepared in a total monomer concentration at 1.0 mmol/g<sub>mixture</sub>.

a high content of  $\beta$ -CD as well (**Figure 1-9b,c**). These results demonstrate that the mechanical properties of hydrogels with various species of polymer matrix can be improved by the incorporation of the supramolecular bonding at the filler/matrix interface.

#### 1-4. Conclusions

In conclusion, composite hydrogels based on cellulose fiber as a filler in which supramolecular bonding was incorporated at the filler/matrix interface were successfully fabricated. In this chapter, the author developed composite hydrogels with great interfacial compatibility by incorporation of the host–guest interaction between cellulose fiber and the matrix utilizing  $\beta$ -CD and Ad. In the hydrogels, Ad-CNF acted as both the filler as well as the multi-point physical cross-linker for the supramolecular bonding. Moreover,  $\beta$ -CDAAm enhanced both dispersibility of Ad-CNF and the interfacial compatibility in the composite hydrogels. Mechanical properties of the hydrogels were improved because the supramolecular bonding at the filler/matrix interface effectively acted as physical cross-linking points of the composite hydrogels. The cleavage of the reversible bonding also sacrificially dissipated mechanical energy when the hydrogels were deformed. The composite hydrogels reinforced with cellulose fiber and the interfacial cross-linking based on the host–guest interaction would expand application potential of hydrogels in biomedical and industrial fields.

#### 1-5. References

- 1. Z. Liu, P. Calvert. Adv. Mater. 2000, 12, 288.
- 2. J. H. Holtz, S. A. Asher. Nature 1997, 389, 829.
- 3. T. R. Hoare, D. S. Kohane. *Polymer* **2008**, *49*, 1993.
- S. Gerecht, J. A. Burdick, L. S. Ferreira, S. A. Townsend, R. Langer, R., G. Vunjak-Novakovic, *Proc. Natl. Acad. Sci. USA* 2007, 104, 11298.
- 5. Y. Okumura, K. Ito, Adv. Mater. 2001, 13, 485.
- T. Sakai, T. Matsunaga, Y. Yamamoto, C. Ito, R. Yoshida, S. Suzuki, N. Sasaki, M. Shibayama, U. I. Chung, *Macromolecules* 2008, 41, 5379.
- 7. J. P. Gong, Y. Katsuyama, T. Kurokawa, Y. Osada, Adv. Mater. 2003, 15, 1155.
- 8. K. Haraguchi, T. Takehisa, Adv. Mater. 2002, 14, 1120.
- 9. W. C. Lin, W. Fan, A. Marcellan, D. Hourdet, C. Creton, *Macromolecules* 2010, 43, 2554.
- 10. G. Gao, G. Du, Y. Sun, J. Fu, ACS Appl. Mater. Interfaces 2015, 7, 5029.

- 11. R. Liu, S. Liang, X. Z. Tang, D. Yan, X. Li, Z. Z. Yu, J. Mater. Chem. 2012, 22, 14160.
- 12. M. Liu, Y. Ishida, Y. Ebina, T. Sasaki, T. Hikima, M. Takata, T. Aida, Nature 2015, 517, 68.
- 13. T. Zhang, T. Zuo, D. Hu, C. Chang, ACS Appl. Mater. Interfaces 2017, 9, 24230.
- 14. R. Kobe, S. Iwamoto, T. Endo, K. Yoshitani, Y. Teramoto, Polymer 2016, 97, 480.
- 15. M. Zhong, Y. T. Liu, X. M. Xie, J. Mater. Chem. B 2015, 3, 4001.
- 16. A. Sahu, W. I. Choi, G. Tae, Chem. Commun 2012, 48, 5820.
- 17. Y. Yang, X. Wang, F. Yang, H. Shen, D. Wu, Adv. Mater. 2016, 28, 7178.
- 18. M. V. Rekharsky, Y. Inoue, Chem. Rev. 1998, 98, 1875.
- 19. A. Harada, Y. Takashima, M. Nakahata, Acc. Chem. Res. 2014, 47, 2128.
- P. Zhang, X. Qian, Z. Zhang, C. Li, C. Xie, W. Wu, X. Jiang, ACS Appl. Mater. Interfaces 2017, 9, 5768.
- 21. S. Mizuno, T. Asoh, Y. Takashima, A. Harada, H. Uyama, *Polym. Degrad. Stab.* **2019**, *160*, 136.
- 22. G. Zhang, Y. Luan, X. Han, Y. Wang, X. Wen, C. Ding, J. Gao, *Green Chem.* 2013, 15, 2081.
- 23. T. Kakuta, Y. Takashima, A. Harada, Macromolecules 2013, 46, 4575.
- 24. N. Lin, A. Dufresne, Biomacromolecules 2013, 14, 871.
- 25. J. H. Kim, B. S. Shim, H. S. Kim, Y. J. Lee, S. K. Min, D. Jang, Z. Abas, J. Kim, *Int. J. of Precis. Eng. and Manuf.-Green Tech.* **2015**, *2*, 197.
- 26. M. Z. Rong, M. Q. Zhang, W. H. Ruan, Mater. Sci. Technol. 2006, 22, 787.
- 27. M. Nogi, H. Yano, Adv. Mater. 2008, 20, 1849.
- 28. X. Cui, T. Honda, T. Asoh, H. Uyama, Carbohydrate Polymers 2020, 230, 115662.
- 29. C. Qian, T. Asoh, H. Uyama, Chem. Commun. 2018, 54, 11320.
- 30. M. Miyauchi, A. Harada, A. J. Am. Chem. Soc. 2004, 126, 11418.
- A. Harada, R. Kobayashi, Y. Takashima, A. Hashidzume, H. Yamaguchi, *Nat. Chem.* 2011, 3, 34.
- 32. E. Ducrot, Y. Chen, M. Bulters, R. P. Sijbesma, C. Creton, Science, 2014, 344, 186.

### Chapter 2

# Thermoresponsive composite hydrogels reinforced with supramolecular cellulose filler

#### 2-1. Introduction

Stimuli-responsive hydrogels have attracted much attention because of their ability to change their functionality in response to the external environment and their wet and soft properties with biocompatibility<sup>1-8</sup>. Poly(*N*-isopropylacrylamide) (PNIPAAm) is the most extensively studied thermoresponsive polymer, which shows temperature-dependent phase transition<sup>9-13</sup>. When the temperature is nearly below its lower critical solution temperature (LCST), the PNIPAAm gel swells owing to the hydration of the polymer network. On the other hand, nearly above the LCST, the gel shrinks because of dehydration of the polymer network due to the enhancement of hydrophobic interactions at elevated temperatures. However, because hydrogels are three-dimensional networks composed of cross-linked hydrophilic polymer chains with high water content, the practical application of conventional chemically cross-linked hydrogels are limited due to their poor mechanical properties. To improve the mechanical strength of gels, composites comprising fillers have been considered<sup>14-20</sup>.

As mentioned in the previous chapter, CNFs, which are suitable candidates for sustainable fillers, have been widely investigated as environmentally friendly reinforcing fibers, both academically and in industry<sup>21-26</sup>. Moreover, hydroxyl groups present on the surface of CNFs allow for a wide range of chemical transformations for accessing composite materials with useful properties<sup>23-27</sup>. To achieve composite materials with excellent mechanical properties, it is important to control the dispersibility of fillers in matrices and the interfacial compatibility between the fillers and matrices. In the previous chapter, the author developed composite hydrogels reinforced with supramolecular fillers based on cellulose fibers<sup>27</sup>. In this system, the dispersibility of the cellulose fiber and the interfacial compatibility between the fiber and matrix were improved simultaneously, resulting in enhanced maximum strength and toughness of the hydrogels. However, the mechanism *via* which fillers operate in stimuli-responsive hydrogels with large volume changes is not known.

In this chapter, the author designed thermoresponsive composite hydrogels reinforced with a supramolecular cellulose filler. To achieve practical applicability of the supramolecular filler as the reinforcing agent of the composite hydrogel, it is essential to investigate the effect of the interfacial host–guest interaction between cellulose fiber and the PNIPPAm network both in the swollen and deswollen states of the hydrogels. For understanding the effect of incorporating host–guest interactions between the filler and matrix into the thermoresponsive hydrogels based on PNIPAAm, which changes its volume in response to temperature, the resulting changes in the mechanical properties at 25 and 50 °C are discussed (**Figure 2-1**).



**Figure 2-1.** Schematic illustration of the thermoresponsive hydrogels reinforced with the supramolecular cellulose filler.

### 2-2. Experimental Section

#### **Materials and Methods**

Cellulose powder was obtained from Nacalai Tesque Inc. *N*-isopropylacrylamide (NIPAAm), *N*,*N*'-methylenebis(acrylamide) (MBAAm), DMAP, and DCC were purchased from FUJIFILM Wako Pure Chemical Corporation. NIPAAm was recrystallized from hexane. 2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone was purchased from Tokyo Chemical Industry Co., Ltd.  $\beta$ -CDAAm was obtained from Yushiro Chemical Industry Co., Ltd. All reagents were used without further purification, unless otherwise stated. AdHex-COOH and  $\beta$ -CD-NH<sub>2</sub> were prepared according to previous reports<sup>28,29</sup>.

#### Measurements

The mechanical properties of the gels were measured by tensile tests using a tensile tester

(Shimadzu EZ-Graph). For the measurement at 25 °C, the tensile test was performed at 30 mm/min in the tensile mode in an ambient atmosphere. For the measurement at 50 °C, the tensile test was performed in water at 50 °C. The toughness of the hydrogels was calculated by integrating the area up to the elongation at break of the stress–strain curves. For the stepwise loading and unloading measurement at 25 °C, the tensile test was performed at 10 mm/min. A single sample was stretched to the strain at 40, 80, 120, 160, 200, and 240%, in this order. The hydrogel was unloaded immediately after reaching a certain strain in each cycle. The stress and strain in loading step were recorded.

#### Preparation of Ad-modified cellulose nanofiber (Ad-CNF)

Ad-CNF was prepared as described in the previous chapter. An aqueous suspension of cellulose powder (1.3 wt%) was used for the aqueous counter collision (ACC) treatment using a Star-Burst Mini (Sugino Machine Ltd., Japan), under an ejecting pressure of 230 MPa with 30 passes, resulting in an aqueous dispersion of CNF (1.9 wt%).

Ad-CNF was synthesized *via* a condensation reaction between the carboxylic group of AdHex-COOH and the hydroxyl group of cellulose fiber. The aqueous dispersions of CNF (1.9 wt%, approximately 15 mL, 245 g in total for this reaction) were diluted with acetone (approximately 20 mL) in 50 mL centrifuge tubes and mixed using a vortex mixer. The dispersions were centrifuged at 9000 rpm, and the supernatant was removed from the mixture. The CNF was redispersed in acetone and centrifuged to remove the supernatant. The dispersion medium was solvent-exchanged with acetone through repeated redispersion and centrifugation (five cycles). The CNF dispersion in acetone was collected in a flask by adding acetone and homogenized by stirring. A small portion of the dispersion was dried in an oven (120 °C, 1 h), and the dry content of the dispersion was determined using gravimetric analysis. AdHex-COOH (2.42 g, 0.4 eq./anhydrous glucose unit, AGU) and DMAP (1.51 g, 0.6 eq./AGU) was dissolved in acetone (50 g), and this solution was added to the CNF dispersion, adjusting the weight% of CNF in acetone to 0.7 wt% in the reaction, and allowed to react for 24 h at room temperature. Methanol was added to quench the reaction, and the dispersion was centrifuged at 9000 rpm to

remove unreacted reagents. To remove *N*,*N*-dicyclohexylurea and other unreacted reagents from the precipitates, the dispersion medium was exchanged with methanol by repeated redispersion and centrifugation (15 cycles). Finally, the dispersion medium was solvent-exchanged to pure water by repeated redispersion and centrifugation (five cycles) to obtain an Ad-CNF aqueous dispersion. The dry content of the dispersion was determined using gravimetric analysis. Drying was performed using a lyophilization machine. The weight ratio of the dispersion was adjusted to 2.2 wt% by adding a suitable amount of pure water. The yield of the dispersion was 169 g. The degree of substitution value of Ad-CNF calculated from C/N ratio in elemental analysis was 0.093.

#### General preparation of composite hydrogels (CD-Ad gels)

Composite hydrogels possessing supramolecular bonding were prepared *via* free-radical copolymerization of NIPAAm and  $\beta$ -CDAAm in the presence of Ad-CNF. The total concentration of monomers was 1.5 mmol/g<sub>mixture</sub>. NIPAAm and  $\beta$ -CDAAm were dissolved in an aqueous dispersion of Ad-CNF (2.0 wt%, 4.0 g). The concentration of Ad group on the surface of Ad-CNF in the pre-gel dispersion mixture, is approximately 1 × 10<sup>-2</sup> mmol/g<sub>mixture</sub>. The molar ratios of  $\beta$ -CDAAm /NIPAAm were 0/100, 1/99, 3/97, 5/95 (CD0-Ad, CD1-Ad, CD3-Ad, and CD5-Ad gels, respectively). MBAAm (6.0 × 10<sup>-3</sup> mmol) as a cross-linking agent and 2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (6.0 × 10<sup>-2</sup> mmol) as an initiator were dissolved in the dispersion, and degassing was performed using a diaphragm pump. The degassed solution was poured into an assembly of glass and silicon elastomer spacer mold. Polymerization was performed in an ice bath for 30 min under UV light irradiation (20 mW/cm<sup>2</sup>), and the mold was flipped every 15 min. The prepared hydrogels were washed with water to remove the unreacted monomer and initiator. For the measurement, the hydrogels were immersed in water at 25 or 50 °C for more than 2 days.

#### Preparation of composite hydrogels using CNF as a filler (CD-CNF gels)

To perform control experiments, composite hydrogels without supramolecular bonding were prepared *via* free-radical copolymerization of NIPAAm and  $\beta$ -CDAAm in the presence of

CNF. The total concentration of monomers was 1.5 mmol/ $g_{mixture}$ . NIPAAm and  $\beta$ -CDAAm were dissolved in the CNF aqueous dispersion (2.0 wt%, 4.0 g). The molar ratios of  $\beta$ -CDAAm/NIPAAm were 0/100, 1/99, 3/97, 5/95 (CD0-CNF, CD1-CNF, CD3-CNF, and CD5-CNF gels, respectively). The other process for the addition of the cross-linking agent and initiator, molding, polymerization, and removal of unreacted monomers and initiator from hydrogels, was the same as that described in the previous section.

#### Preparation of composite hydrogels in the presence of inhibitors

To perform inhibition tests, the composite hydrogels were prepared by the copolymerization of the monomers in the presence of  $\beta$ -CD-NH<sub>2</sub> as the competitor of the supramolecular bonding between the filler and the matrix.  $\beta$ -CD-NH<sub>2</sub> (410 mg, 0.36 mmol) was dissolved in the pre-gel dispersion mixture of the CD3-Ad gel (CD3-Ad +  $\beta$ -CD-NH<sub>2</sub> gel). The remaining conditions were the same as for the preparation of the CD-Ad gels.

#### Measurement of water content of the hydrogels

To determine the water content of the hydrogel, gravimetric analysis was conducted. The hydrogels were kept at 25 or 50 °C for more than 2 days and weighed after removal of surface water. Water content was calculated using Eq. 2-1:

water content (%) = 
$$\frac{W_1 - W_0}{W_1} \times 100$$
 (2-1)

where  $w_0$  is the weight of the hydrogel after drying by lyophilization, and  $w_1$  is the weight of the hydrogel before drying.

#### Swelling-Deswelling behavior of the hydrogels

For the measurement of swelling-deswelling kinetics, disk-shaped CD-Ad and CD-CNF gels were first stored at a predetermined temperature (25 or 50 °C) for more than 2 days in water to reach the equilibrium state. The gels were quickly transferred into water at 50 °C and 25 °C. The diameter of the gels was recorded at a certain elapsed time, and the swelling behavior

was evaluated by calculating the ratio of the diameter (D) to the initial diameter  $(D_0)$ .

To measure the equilibrium swelling ratio of the hydrogels at different temperatures, diskshaped hydrogels were first immersed in water at 25 °C for more than 2 days. Gels were transferred into water at particular temperatures for 3 days, and the swelling ratio was evaluated based on the diameter of the gels.

#### 2-3. Results and discussion

#### Thermoresponsive properties of the composite hydrogels

CD-Ad gels with host–guest interactions at the cellulose fiber/matrix interface were fabricated *via* the copolymerization of NIPAAm, MBAAm, and  $\beta$ -CDAAm, in the presence of Ad-modified cellulose nanofiber (Ad-CNF) as the filler (**Figure 2-2a**). This *in situ* copolymerization enables the formation of an inclusion complex between  $\beta$ -CDAAm and Ad on the surface of the cellulose fiber, resulting in the enhancement of the hydrogel's mechanical properties due to the increase in the number of their physical cross-linking points (**Figure 2-2b,c**). In CD*x*-Ad gels, *x* represents the feed molar percentage of  $\beta$ -CDAAm. At 25 °C, the hydrogel swelled well and retained a large amount of water, because the network structure of the hydrogel was hydrated below the LCST (**Figure 2-3a**). When the temperature was at 50 °C, the hydrogel shrunk and its size decreased. Additionally, the equilibrium of the volume phase transition of the hydrogel was measured at varying temperatures (**Figure 2-3b**). The hydrogel

continued shrinking as the temperature increased, and the swelling ratio decreased significantly above 40 °C, which is above the LCST of PNIPAAm. The swelling and deswelling behavior of the CD3-Ad gel after a temperature jump from 25 °C to 50 °C, and from 50 °C to 25 °C is



**Figure 2-2.** Chemical structure of (a) Ad-CNF and (b) the CD-Ad gel matrix. (c) Preparation of CD-Ad gel.

shown in **Figure 2-3c,d**, respectively. Based on these results, it can be concluded that this composite hydrogel reinforced with a supramolecular filler demonstrates thermoresponsive properties of hydrogels, similar to typical PNIPAAm hydrogels.



**Figure 2-3.** (a) Photographs of the CD3-Ad gel at 25 and 50 °C. (b) Swelling equilibrium of CD3-Ad gel at varying temperatures. (c) Deswelling behavior of CD3-Ad gel after a temperature jump from 25 °C to 50 °C. (d) Swelling behavior of CD3-Ad gel after a temperature jump from 50 °C to 25 °C.

#### Mechanical properties of the composite gels at swelling state

The mechanical properties of the hydrogels measured at 25 °C are shown in **Figure 2-4** and **Table 2-1**. In CD-Ad gels, the maximum stress increased significantly with increasing in-feed molar ratio of  $\beta$ -CDAAm, and its maximum value was 47 ± 4 kPa for the CD5-Ad gel (**Figure 2-4a**). This enhancement of mechanical properties resulted chiefly from two factors: the improvement of both the dispersibility of the filler in the matrix and the compatibility between the filler and the matrix. As described in the previous chapter, the dispersibility of Ad-CNF differed drastically in the presence and absence of  $\beta$ -CD. Ad-CNF itself has a hydrophobic Ad

group, leading to aggregation of fiber the in the aqueous dispersion. Meanwhile, with the addition of β-CD, the hydrophilicity of the surface of Ad-CNF improved due to the inclusion of the hydrophobic Ad group in the hydrophilic  $\beta$ -CD molecule, thereby enhancing the dispersibility of Ad-CNF (Figure 2-2c). The formation of the hostguest complex on the surface of cellulose fiber was achieved simply by mixing Ad-CNF with



**Figure 2-4.** Schematic drawing and stress–strain curves of (a) CD-Ad and (b) CD-CNF gels. Tensile test of the swollen hydrogels was performed at 25 °C.

 $\beta$ -CD in aqueous medium. Moreover, this enabled the introduction of the host–guest complex on the surface of the filler during the preparation of the composite hydrogel.  $\beta$ -CDAAm, as the precursor of the matrix, readily bound to Ad on Ad-CNF in the pre-gel dispersion before polymerization. Therefore, the subsequently fabricated hydrogels also retained the physical cross-linking points of the host–

guest complex during *in situ* polymerization. In this manner, the maximum stress of CD-Ad gels increased with an increase in the molar ratio of  $\beta$ -CDAAm owing to the favorable filler/matrix compatibility and dispersibility of the filler in the matrix. Moreover, even after the shrinking and reswelling



**Figure 2-5.** (a) Stress–strain curves of CD3-Ad gel (green) and CD3-Ad gel after heating at 50 °C for 3 days followed by cooling at 25 °C for 3 days (red). (b)Stress–strain curves of CD3-Ad gel and CD3-Ad gel prepared in the presence of  $\beta$ -CD-NH<sub>2</sub> as an inhibitor (2 eq. to  $\beta$ -CDAAm).

processes of the hydrogel, no significant changes in the mechanical properties were observed (**Figure 2-5a**). This result indicates that the supramolecular bonding at the filler/matrix interface was maintained during the swelling and deswelling processes. In contrast, the stress–strain curves of composite hydrogels with unmodified CNF as the filler, shown in **Figure 2-4b**, revealed that no significant improvement was observed in the maximum stress of the CNF-reinforced hydrogels. In addition, the stress–strain curves of the CD3-Ad gels revealed a marked decrease in the tensile strength when  $\beta$ -CD-NH<sub>2</sub> was present as a competitive inhibitor (**Figure 2-5b**). These results indicate that the hydrogels were not significantly reinforced without supramolecular bonding between the filler and matrix.

	e				
Samples Wate	Water content	σ	3	Ε	Toughness
	%	kPa	%	kPa	kJ m <sup>-3</sup>
CD0-Ad	95	$14 \pm 1$	$275\pm 19$	$5.5\pm0.5$	$22\pm3$
CD1-Ad	94	$21\pm2$	$271\pm22$	$6.7\pm0.7$	$32\pm3$
CD3-Ad	92	$38\pm2$	$232\pm15$	$13 \pm 1$	$50\pm4$
CD5-Ad	90	$47\pm4$	$180\pm8$	$16 \pm 1$	$43 \pm 5$
CD0-CNF	95	$11\pm2$	$211\pm22$	$5.7\pm0.6$	$12 \pm 2$
CD1-CNF	95	$9.2\pm0.8$	$202\pm 6$	$4.8\pm0.3$	$9.7\pm0.5$
CD3-CNF	94	$12\pm2$	$165\pm14$	$7.4\pm0.1$	$10\pm 2$
CD5-CNF	92	$13 \pm 1$	$154\pm9$	$8.6\pm0.3$	$10\pm1$

**Table 2-1.** Water content, maximum stress ( $\sigma$ ), elongation at break ( $\varepsilon$ ), Young's modulus (*E*), and toughness of CD-Ad and CD-CNF gels at 25 °C.

#### Mechanical properties of the composite gels at deswelling state

The mechanical properties of the deswollen hydrogel above the LCST were also investigated. Tensile measurements of the hydrogels were performed in water at 50 °C to prevent drying. As shown in **Figure 2-6**, the maximum stress and breaking strain of the hydrogels increased significantly compared to the values at 25 °C. The maximum stress and breaking strain of the CD3-Ad gel were  $570 \pm 20$  kPa and  $936 \pm 25\%$ , respectively. This is because hydrogels were deswollen above the LCST, and the density of the polymer increased with decreasing water content. In contrast to the case of CD-Ad gels at 25 °C, the mechanical

properties at 50 °C did not change as the amount of  $\beta$ -CD in the matrix increased. On the other hand, CD-CNF gels exhibited mechanical properties that differed compared to those of CD-Ad gels. The maximum stress and elongation at break were similar for the CD0-CNF and CD-Ad gels, although the mechanical strength of CD0-CNF at 25 °C was inferior to that of



**Figure 2-6.** Schematic drawing and stress–strain curves of (a) CD-Ad and (b) CD-CNF gels. Tensile test of the deswollen hydrogels was performed at 50  $^{\circ}$ C in water.

CD-Ad gels with host-guest interactions. This is probably because when the hydrogels shrunk, their mechanical properties were dominated by the strength of the matrix with high polymer density<sup>30</sup>. Additionally, in contrast to CD-Ad gels, the mechanical properties of CD-CNF with  $\beta$ -CD deteriorated significantly at a higher  $\beta$ -CD content. This decrease in the maximum stress likely arises from the incorporation of the hydrophilic β-CD moiety in the matrix, leading to hydration of the matrix. The water content of CD-CNF gels increased as the amount of  $\beta$ -CD increased, indicating that the degree of hydration increased with the incorporation of  $\beta$ -CD in the matrix (Table 2-2). Based on these results, it can be concluded that the lack of a significant deterioration in the mechanical properties of the CD-Ad gels with increasing  $\beta$ -CD content can be ascribed chiefly to the interfacial host-guest interactions between the filler and matrix. In other words, the physical cross-linking of the host-guest complex in CD-Ad gels formed even when the hydrogels shrunk at temperatures above their LCST and contributed to the reinforcement of the hydrogels<sup>30</sup>. The interfacial supramolecular bonding acted as the crosslinking points of the hydrogels, leading to a high polymer density of the swollen hydrogels and improved maximum stress at approximately 600 kPa. Additionally, the elongation at break was maintained at a high value, which was approximately 1000%, probably because the host-guest complex was able to dissociate sacrificially when the hydrogels were stretched.

Comular	Water content	σ	3	Ε	Toughness
Samples	%	kPa	%	kPa	10 <sup>3</sup> kJ m <sup>-3</sup>
CD0-Ad	40	$600\pm50$	$1095\pm81$	$350\pm40$	$3.7\pm 0.2$
CD1-Ad	35	$610\pm40$	$1075\pm101$	$410\pm40$	$3.8\pm 0.4$
CD3-Ad	34	$570\pm20$	$936\pm25$	$310\pm30$	$3.2\pm 0.2$
CD5-Ad	37	$490\pm50$	$819\pm82$	$220\pm60$	$2.3\pm0.3$
CD0-CNF	39	$580\pm20$	$934\pm84$	$490\pm40$	$3.3\pm 0.4$
CD1-CNF	44	$410\pm40$	$1135\pm143$	$310\pm60$	$2.8\pm0.5$
CD3-CNF	44	$260\pm30$	$899\pm58$	$170\pm40$	$1.4\pm0.1$
CD5-CNF	47	$190\pm10$	$702\pm83$	$120\pm10$	$0.81\pm0.13$

**Table 2-2.** Water content, maximum stress ( $\sigma$ ), elongation at break ( $\varepsilon$ ), Young's modulus (*E*), and toughness of CD-Ad and CD-CNF gels at 50 °C.

#### Young's modulus and toughness of the composite hydrogels

The relationship between Young's modulus and toughness of composite hydrogels is summarized in **Figure 2-7**. The toughness of CD-Ad gels swollen at 25 °C increased at higher molar ratios of  $\beta$ -CDAAm (**Figure 2-7a**), with CD3-Ad gel being the toughest, with a value of  $50 \pm 4$  kJ m<sup>-3</sup>. In addition, the Young's



**Figure 2-7.** Relationship between Young's modulus and toughness of composite hydrogels, (a) swollen at 25  $^{\circ}$ C and (b) deswollen at 50  $^{\circ}$ C.

modulus of the hydrogels also increased from 5.5 to 16 kPa with an increase in the concentration of  $\beta$ -CDAAm from 0 to 5.0 mol%. In contrast to this behavior of CD-Ad gels, no significant improvement in toughness and Young's modulus was observed at higher  $\beta$ -CD contents in the control experiments where unmodified CNF was used as the filler of the composite hydrogels. Therefore, these results indicate that supramolecular bonding enhances the compatibility between the filler and matrix. It effectively acted as a physical cross-linking point for the CD-Ad gels. Furthermore, the cleavage of reversible bonds also dissipated mechanical energy sacrificially when the hydrogels were deformed<sup>31</sup>. This is also supported by a result of a stepwise loading and unloading measurement for CD3-Ad gel<sup>32</sup> (**Figure 2-8**).



Moreover, the toughness and Young's modulus of the CD-Ad gels deswollen at 50 °C did not decrease significantly with an increase in the ratio of  $\beta$ -CD in the matrix, except for CD5-Ad gel (**Figure 2-7b**). On the other hand, those of the CD-CNF gels decreased significantly with an increase in the  $\beta$ -CD ratio in the matrix. The highest toughness at 25 °C was observed for

**Figure 2-8.** Stress—strain curves of a single sample of CD3-Ad gel in stepwise loading and unloading measurement

the CD3-Ad gel, being  $3200 \pm 200$  kJ m<sup>-3</sup>. The toughness of the CD3-CNF gel was  $1400 \pm 100$  kJ m<sup>-3</sup>, which is more than two-fold lower than that of the CD3-Ad gel. The CD3-Ad gel demonstrated an appreciable reinforcing effect at both 25 and 50 °C. Similarly, the toughness and Young's modulus of all the CD-Ad gels, except CD0-Ad gel, was higher than that of CD-CNF gels prepared using the same molar ratios of  $\beta$ -CD as the matrix, possibly due to the enhancement of interfacial compatibility between the filler and the matrix through host–guest interactions. By incorporating a host–guest complex at the filler/matrix interface utilizing Ad-CNF as a supramolecular filler, the mechanical properties of the thermoresponsive polymer were enhanced compared to those of the hydrogel without supramolecular bonding.

#### 2-4. Conclusions

In summary, thermoresponsive composite hydrogels based on PNIPAAm reinforced with Ad-CNF as a supramolecular filler were successfully fabricated. In this chapter, the author revealed the effect of host–guest interactions between  $\beta$ -CD and Ad at the filler/matrix interface in the swelling and deswelling system of the hydrogels. At swelling states below the LCST, interfacial supramolecular bonding contributed substantially to the enhancement of the maximum stress of the hydrogels. Additionally, the toughness of the hydrogels was also improved owing to energy dissipation resulting from the sacrificial dissociation of the host–guest complex under applied stress. Moreover, even when the hydrogels shrunk above their

LCST, the host–guest interaction also acted as a physical cross-linking point in the hydrogels. This led to a high polymer density in the matrix of the composite hydrogels. As a result, the maximum stress and elongation at break of the composite hydrogels were enhanced compared to the hydrogels without host–guest interactions. The present stimuli-responsive composite hydrogels reinforced with supramolecular cellulose filler, offering interfacial cross-linking based on host–guest interactions, is expected expand the utility of hydrogels in biomedical and engineering materials.

#### 2-5. References

- 1. Z. Liu, P. Calvert, Adv. Mater. 2000, 12, 288.
- 2. J. H. Holtz, S. A. Asher, Nature 1997, 389, 829.
- 3. T. R. Hoare, D. S. Kohane, *Polymer* **2008**, *49*, 1993.
- S. Gerecht, J. A. Burdick, L. S. Ferreira, S. A. Townsend, R. Langer, and G. Vunjak-Novakovic, *Proc. Natl. Acad. Sci. USA* 2007, 104, 11298.
- 5. M. Liu, Y. Ishida, Y. Ebina, T. Sasaki, T. Hikima, M. Takata, T. Aida, Nature 2015, 517, 68.
- 6. Y. Qiu, K. Park, Adv. Drug Deliv. Rev. 2001, 53, 321.
- 7. Tokarev, S. Minko, Soft Matter 2009, 5, 511.
- J. Sasaki, T. Asoh, T. Matsumoto, H. Egusa, T. Sohmura, E. Alsberg, M. Akashi, H. Yatani, *Tissue Eng. Part A* 2010, 16, 2497.
- 9. Y. Hirokawa, T. Tanaka, J. Chem. Phys. 1984, 81, 6379.
- 10. H. G. Schild, Prog. Polym. Sci. 1992, 17, 163.
- 11. Y. Kaneko, K. Sakai, A. Kikuchi, R. Yoshida, Y. Sakurai, T. Okano, *Macromolecules* **1995**, 28, 7717.
- 12. X. S. Wu, A. S. Hoffman, P. Yager, J. Polym. Sci., Part A 1992, 30, 2121.
- A. Sugawara, T. Asoh, Y. Takashima, A. Harada, H. Uyama, ASC Macro Lett. 2021, 10, 971.
- 14. K. Haraguchi, T. Takehisa, Adv. Mater. 2002, 14, 1120.
- 15. R. Liu, S. Liang, X. Z. Tang, D. Yan, X. Li, Z. Z. Yu, J. Mater. Chem. 2012, 22, 14160.
- 16. Q. Wang, R. Hou, Y. Cheng, J. Fu, Soft Matter 2012, 8, 6048.
- 17. G. Gao, G. Du, Y. Sun, J. Fu, ACS Appl. Mater. Interfaces 2015, 7, 5029.
- T. Huang, H. G. Xu, K. X. Jiao, L. P. Zhu, H. R. Brown, H. L. Wang, *Adv. Mater.* 2007, *19*, 1622.
- 19. T. Yamamoto, T. Asoh, H. Uyama, Sci. Rep. 2020, 10, 17173.
- 20. P. Thoniyot, M. J. Tan, A. A. Karim, D. J. Young, X. J. Loh, Adv. Sci. 2015, 2, 1400010.
- T. Li, C. Chen, A. H. Brozena, J. Y. Zhu, L. Xu, C. Driemeier, J. Dai, O. J. Rojas, A. Isogai, L. Wågberg, L. Hu, *Nature* 2021, 590, 47.

- 22. M. Nogi, H. Yano, Adv. Mater. 2008, 20, 1849.
- 23. R. Kobe, S. Iwamoto, T. Endo, K. Yoshitani, Y. Teramoto, Polymer 2016, 97, 480.
- 24. T. Zhang, T. Zuo, D. Hu, C. Chang, ACS Appl. Mater. Interfaces 2017, 9, 24230.
- 25. G. Sinawang, T. Asoh, M. Osaki, H. Yamaguchi, A. Harada, H. Uyama, Y. Takashima, *ACS Appl. Polym. Mater.* **2020**, *2*, 2274.
- 26. X. Cui, T. Hiraoka, T. Honda, Y. Hsu, T. Asoh, H. Uyama, *Compos. Sci.; Technol.* 2021, 202, 108595.
- 27. A. Sugawara, T. Asoh, Y. Takashima, A. Harada, H. Uyama, *Polym. Degrad. Stab.* **2020**, *177*, 109157.
- 28. M. Osaki, S. Yonei, C. Ueda, R. Ikura, J. Park, H. Yamaguchi, A. Harada, M. Tanaka, Y. Takashima, *Macromolecules* **2021**, *54*, 8067.
- 29. T. Kakuta, Y. Takashima, A. Harada, Macromolecules 2013, 46, 4575.
- 30. M. Miyauchi, A. Harada, A. J. Am. Chem. Soc. 2004, 126, 11418.
- 31. A. Harada, R. Kobayashi, Y. Takashima, A. Hashidzume, H. Yamaguchi, *Nat. Chem.* **2011**, *3*, 34.
- 32. E. Ducrot, Y. Chen, M. Bulters, R. P. Sijbesma, C. Creton, Science 2014, 344, 186.

# **Chapter 3**

# Mechano-responsive hydrogels driven by the sacrificial dissociation of a host–guest inclusion complex

#### 3-1. Introduction

Mechano-responsive materials exhibit their functions when subjected to external stress<sup>1,2</sup>. For example, mechanochromic materials, which change their color in response to mechanical stress, have attracted much attention because of their ability to visualize applied stress in materials<sup>3-14</sup>. Changes in the molecular structure of mechanophores<sup>3-6</sup>, deformation of photonic crystals<sup>7-10</sup>, and transformation of self-assembled structures<sup>11-14</sup> are well-known methods by which color change can be visualized. By enabling the detection of damage accumulating within materials, major breakage can be prevented.

As described in the previous sections, supramolecular bonds, such as host–guest interactions, are often utilized as bonds that break when stress is applied. CDs have strong complexing abilities with various organic guest molecules in aqueous media, and have found widespread applications in many fields<sup>15-20</sup>. Supramolecular materials, including hydrogels that incorporate CDs, exhibit specific mechanical properties such as toughness, elasticity, stretchability, stress recovery, and self-healing properties<sup>21,22</sup>. These functions are expressed by the reversible formation and dissociation of the host–guest complex. If the conformations of polymer chains can be controlled by the disruption of host–guest interactions, the creation of mechano-responsive materials can be achieved using the application of stress as a switch.

It is convenient to utilize the coil–globule transition of thermoresponsive polymers to cause significant structural changes in these polymers. PNIPAAm is a thermoresponsive polymer that exhibits a coil–globule transition around its LCST<sup>23-26</sup>. The LCST of thermoresponsive polymers strongly depends on the balance between the hydrophobicity and hydrophilicity of the polymer. The LCST is decreased by the copolymerization of NIPAAm with a hydrophobic monomer<sup>27-29</sup>. PNIPAAm copolymers are prepared by the copolymerization of NIPAAm with a hydrophobic distribution of a hydrophobic guest in hydrophilic CD increases their LCST<sup>30,31</sup>. In a system

wherein a temperature-responsive polymer with a guest group is introduced into a polymer network with a host molecule, the dissociation of the supramolecular bonds of the host–guest complex is achieved by applying mechanical stress. This leads to the exposure of the hydrophobic group, thus decreasing the LCST of the thermoresponsive polymer and inducing the phase transition of the polymer.

In this chapter, the author reports the fabrication of a mechano-responsive hydrogel exhibiting stress-induced phase transition by using a combination of a thermoresponsive polymer and host–guest inclusion complex formed between  $\beta$ -CD and Ad. Poly(NIPAAm-*co-N*-adamantylacrylamide), as a thermoresponsive polymer with a guest group, was fixed in a hydrogel with the host group in its network. The thermoresponsive properties of the thermoresponsive guest polymer incorporated in the host hydrogel were suppressed owing to its immobilization on the network, whereas the phase transition was caused by the application of stress. The turbidity changed only at the stressed part and returned to its original state by cooling, which showed that this process could be reversed (**Figure 3-1**).



**Figure 3-1.** Schematic drawing of the mechano-responsive hydrogels driven by the dissociation of the host–guest complex.

#### **3-2. Experimental Section**

#### Materials

NIPAAm, DMAAm, MBAAm, *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TEMED), and 2,2'-azobis(isobutyronitrile) (AIBN) were purchased from FUJIFILM Wako Pure Chemical Corporation. Ammonium persulfate (APS) was purchased from Sigma-Aldrich. DMF was

purchased from Nacalai Tesque.  $\beta$ -CDAAm and *N*-adamantylacrylamide (AdAAm) were obtained from Yushiro Chemical Industry Co., Ltd.  $\beta$ -CD-NH<sub>2</sub> was prepared according to a previously reported procedure<sup>32</sup>. NIPAAm was purified by recrystallization from hexane, and AIBN was recrystallized from methanol. All other chemicals were used as received unless specified otherwise.

# Preparation of poly(*N*-isopropylacrylamide-*co-N*-adamantylacrylamide) (P(NIPAAm-*co*-AdAAm))

P(NIPAAm-*co*-AdAAm) (**Figure 3-3a**) was synthesized *via* free-radical copolymerization. The procedure for the synthesis of the P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) polymer is described below as an example. In P(NIPAAm<sub>x</sub>-*co*-AdAAm<sub>y</sub>), *x* and *y* represent the feed molar ratios of NIPAAm and AdAAm, respectively, to the total monomers. First, NIPAAm (4.3 g, 38 mmol), AdAAm (408 mg, 2.0 mmol), and AIBN (33 mg, 0.20 mmol) were dissolved in DMF (40 mL). The solution was bubbled with N<sub>2</sub> and allowed to react at 70 °C for 24 h. The resultant polymer was purified by dialysis with methanol for 3 days. Subsequently, methanol was removed from the solution, and the precipitate was dissolved in water at a low temperature. P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) was obtained after lyophilization of the aqueous solution (3.5 g, 74%).

#### Fabrication of mechano-responsive hydrogels

The hydrogels were prepared by the free-radical copolymerization of monomers and a cross-linker in the presence of P(NIPAAm-*co*-AdAAm) (**Figure 3-3b**). Herein, the procedure for the fabrication of a hydrogel using P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) with 5.0 mol% of  $\beta$ -CDAAm to that of DMAAm is described as a typical method.  $\beta$ -CDAAm (62 mg) was dissolved in 2.53 g of stock solution, which comprised water (20 g), DMAAm (1.98 g, 20 mmol), MBAAm (31 mg, 0.2 mmol), and APS (45 mg, 0.2 mmol). P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) (406 mg, 15 wt%) was dissolved in the solution in an ice bath. The solution was centrifuged at 9000 rpm for 15 min to remove air bubbles. Subsequently, the solution was degassed using a diaphragm pump, and centrifugation was performed again for 5 min. TEMED (3.45  $\mu$ L, 23  $\mu$ mol) was mixed into the pre-cooled solution in an ice bath, and the solution was poured into a mold (5 × 5 × 0.1 cm)

made of glass plates and a silicone rubber spacer. The solution was allowed to stand overnight in an ice bath. The resultant hydrogel was collected, immersed in deionized water, and stored at 4 °C. The water was changed several times to remove the unreacted chemicals and impurities from the hydrogel. The hydrogel was kept at room temperature for several hours prior to analysis.

#### Measurement of water content of the hydrogels

To determine the water content of the hydrogel, gravimetric analysis was conducted. The hydrogels were kept at room temperature and weighed after removal of surface water. Water content was calculated using Eq. 3-1:

water content (%) = 
$$\frac{W_1 - W_0}{W_1} \times 100$$
 (3-1)

where  $w_0$  is the weight of the hydrogel after drying by lyophilization and  $w_1$  is the weight of the hydrogel before drying.

#### Measurement of the thermoresponsivity of P(NIPAAm-co-AdAAm)

The thermoresponsivity of P(NIPAAm-*co*-AdAAm) was analyzed by measuring the temperature dependence of the transmittance at a wavelength of 700 nm using a spectrophotometer (Jasco V-750, Japan). The heating rate was 0.5 °C/min. The concentration of P(NIPAAm-*co*-AdAAm) was 1.0 wt%. The amount of  $\beta$ -CD-NH<sub>2</sub> was adjusted in accordance with the feed molar amount of Ad in P(NIPAAm-*co*-AdAAm). The temperature at which 50% transmittance of the solution was observed was defined as the LCST.

#### Characterization of P(NIPAAm-co-AdAAm)

The molecular weight and polydispersity of P(NIPAAm-*co*-AdAAm) were determined by size exclusion chromatography (SEC) [column: TSK-gel guardcolumn  $\alpha$  +TSK-gel  $\alpha$ -M + TSK-gel  $\alpha$ -M (Tosoh, Japan) at 40 °C using DMF containing 10 mM LiCl as an eluent, system: SD-8022 degasser, AS-8020 auto-sampler, DP-8020 pump, CO-8020 column oven, and RI-

8020 refractive index detector. (Tosoh, Japan)]. Polystyrene was used as a molecular weight standard. A sample polymeric solution was 10 mg/mL, and the injection volume was 50  $\mu$ L. <sup>1</sup>H NMR spectra were recorded in DMSO-*d*<sub>6</sub> using a JNM-ECS400 (400 MHz, JEOL, Japan).

#### Evaluation of mechano-responsive properties of hydrogels

The hydrogel was subjected to compression tests using a rheometer (HAAKE RheoStress 6000, Thermo Fisher Scientific, USA). For most tests, the testing temperature was set at 37 °C and the compression speed was 3.0 mm/min. The specimens were compressed to specific ratios, maintained in their compressed states for 1 min, and subsequently unloaded. The transparency of the hydrogel was analyzed using a UV–vis spectrophotometer (Jasco V-750, Japan). The transmittance of the specimens through a 1 cm quartz sample cell was recorded in the wavelength range 400–800 nm. The baseline was obtained using deionized water. For the measurement, planar-shaped hydrogels were cut into samples of  $3 \times 9$  mm (thickness was approximately 1 mm) and were kept standing against the wall of a quartz cell filled with deionized water. The plane of the hydrogel samples was perpendicular to the optical path. The measuring temperature was set at 37 °C unless otherwise noted. The signal-to-noise ratio was calculated by dividing the absorbance at 400 nm after compression of the sample by the initial absorbance.

#### Measurement of rheological property of the hydrogels

The rheological property of the hydrogel was analyzed using a rheometer (HAAKE RheoStress 6000, Thermo Fisher Scientific, USA) equipped with P20 Ti L as a measuring geometry. The measurement was performed in controlled stress (CS) mode ( $\tau$  at 10 Pa, temperature at 37 °C, and frequency from 0.1 to 10 Hz).

#### Measurement of tensile property of the hydrogels

Tensile property of the hydrogels was measured by tensile tests using a tensile tester (Shimadzu EZ-Graph, Shimadzu Corporation, Japan). The test was performed at 10 mm/min and the hydrogels were stretched in water at 37 °C.

#### 3-3. Results and discussion

#### Thermoresponsive properties of P(NIPAAm-co-AdAAm)

P(NIPAAm-*co*-AdAAm) exhibited obvious temperature-induced phase transition, comparable to that of PNIPAAm homopolymer (**Figure 3-2a**). The LCST of P(NIPAAm-*co*-AdAAm) decreased with an increase in the concentration of Ad. Specifically, the LCSTs of P(NIPAAm<sub>99</sub>-*co*-AdAAm<sub>1</sub>), P(NIPAAm<sub>97</sub>-*co*-AdAAm<sub>3</sub>), P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>), and P(NIPAAm<sub>93</sub>-*co*-AdAAm<sub>7</sub>) were 29, 26, 23, and 20 °C, respectively (**Figure 3-2b**). Generally, the LCST of thermoresponsive polymers depends on the hydrophobicity of the functional groups on the side chains of the polymers. In P(NIPAAm-*co*-AdAAm), the hydrophobic Ad group was incorporated into the PNIPAAm copolymer; therefore, a decrease in the cloud temperature compared with that of PNIPAAm was observed. Additionally, molecular weight and polydispersity index of these thermoresponsive polymers were similar to each other (**Table 3-1**). On the other hand, Addition of β-CD-NH<sub>2</sub> in P(NIPAAm-*co*-AdAAm) solution led to an increase in the LCST. When 125 mol% of β-CD-NH<sub>2</sub> to that of the Ad group was added to the P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) solution, the cloud temperature increased to 29 °C. This is because the hydrophobic Ad group was covered with hydrophilic β-CD by host–guest interaction. Therefore, apparent hydrophilicity of the thermoresponsive polymer was enhanced.



**Figure 3-2.** (a) Photographs of P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) in an aqueous medium at 10 and 30 °C. Temperature dependence of the transmittance of (b) P(NIPAAm-*co*-AdAAm) prepared with 1.0, 3.0, 5.0, and 7.0 mol% of AdAAm in feed ratio, and (c) P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) in aqueous solution with different molar ratios of  $\beta$ -CD-NH<sub>2</sub> to Ad (0, 25, 50, 75, 100, and 125%).

Sample	Ad (mol%) <sup><i>a</i></sup>	$M_{ m w}$ $^b$	$M_{ m w}/M_{ m n}$
P(NIPAAm99-co-AdAAm1)	1.1	$6.6  imes 10^4$	2.3
P(NIPAAm97-co-AdAAm3)	2.7	$6.6  imes 10^4$	2.5
P(NIPAAm <sub>95</sub> -co-AdAAm <sub>5</sub> )	5.0	$6.3  imes 10^4$	2.8
P(NIPAAm <sub>93</sub> -co-AdAAm <sub>7</sub> )	6.8	$6.7  imes 10^4$	2.4

Table 3-1. The ratio of Ad group in P(NIPAAm-co-AdAAm) and their molecular weights.

<sup>a</sup> observed by <sup>1</sup>H NMR

<sup>b</sup> measured by SEC

#### Mechano-responsive behavior of the hydrogels

The hydrogel comprised a thermoresponsive P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) linear polymer with guest groups and a non-thermoresponsive 3D cross-linked polymer network with host groups, thus possessing a structure similar to that of semi-interpenetrating networks. However, P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) was immobilized in the hydrogel via physical cross-linking owing to the host–guest interactions between  $\beta$ -CD in the hydrogel matrix and Ad in the linear polymer. In the fabrication of the hydrogels, the concentration of DMAAm at 1.0 mol L<sup>-1</sup> and molar ratio of MBAAm to DMAAm at 1.0 mol% exhibited good compression property of the obtained hydrogels, therefore, this condition was selected for further evaluation. The turbidity of the hydrogels before and after compression was observed macroscopically and measured using a spectrophotometer (Figure 3-3c,d). The hydrogels showed high transparency at 25 °C, indicating the random coil structure of P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) (Figure 3-3c-i). When the hydrogel was immersed in water at 37 °C, a temperature that is higher than the LCST of P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>), it became slightly cloudy (Figure 3-3c-iii). This result contrasts with the finding that P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) aqueous solutions exhibit significant phase transition phenomena above the LCST. The LCST of P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) was 23 °C, which is lower than that of the PNIPAAm homopolymer (LCST is approximately 32 °C<sup>23</sup>.) (Figure 3-2b). Even when the hydrogel was heated to 50 °C, no further decrease was observed in the transmittance (Figure 3-3c-v). This is probably because supramolecular bonding, by host-guest interactions between Ad in P(NIPAAm-co-AdAAm) and \beta-CD in the hydrogel, not only increased the LCST of the thermoresponsive polymer but also restricted the

conformational change of P(NIPAAm-co-AdAAm) and the accompanying phase transition.

Interestingly, when mechanical force was applied to the hydrogel by compression at 37 °C, the transparency of the hydrogel decreased, and the transmittance of the spectrum at 400 nm was 68%, although no obvious decrease in transmittance was observed after compression at 25 °C (**Figure 3-3c-ii,iv**). In addition, the spectrum of the hydrogel at 50 °C was almost the same as that obtained at 37 °C before compression (**Figure 3-3d**). Besides, the size of the hydrogels was almost unchanged under different temperatures at 25, 37, and 50 °C. This result indicates that a significant decrease in the transmittance was induced not by simple heating, but by the application of mechanical force at a temperature above the LCST.



**Figure 3-3.** (a) Chemical structure of P(NIPAAm-*co*-AdAAm). (b) Synthesis of the hydrogel. (c) Photographs of the hydrogels, prepared using P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) with 5.0 mol% of  $\beta$ -CDAAm, at (i) 25 °C, (ii) 25 °C after 70% compression, (iii) 37 °C, (iv) 37 °C after 70% compression, (v) 50 °C, and (vi) 50 °C after 70% compression. (d) Transmittance of the hydrogel at 25 °C (blue), 37 °C (black), 50 °C (green), 37 °C after 70% compression (red), and 50 °C after 70% compression (orange).

Therefore, the stress-induced dissociation of the host–guest bond successfully induced the phase transition of the thermoresponsive polymer.

#### Effect of the component of the hydrogels on the mechano-response

As the phase transition can be induced by applying stress, a pattern can be formed by stamping. A star-shaped stamp was used for compression to improve the contrast between the unstressed and stressed areas. In some hydrogels, only the area to which pressure was applied became less transparent, representing clear mechano-responsiveness (Figure 3-4). The effect of the components of the hydrogel on the transmittance was evaluated. First, the hydrogels prepared using P(NIPAAm-co-AdAAm) with different ratios of Ad and fixed amounts of β-CD (5.0 mol% with respect to that of DMAAm) were evaluated to investigate the effect of the amount of Ad in P(NIPAAm-co-AdAAm) on the transmittance of the hydrogels (Figure 3-4a). The unpressed areas exhibited higher transparency in the hydrogels fabricated using larger amounts of Ad in P(NIPAAm-co-AdAAm). This result is opposite to the trend observed in the solution, wherein P(NIPAAm-co-AdAAm) with a larger amount of Ad demonstrated lower solubility in water due to the enhancement of hydrophobicity. On the other hand, when the thermoresponsive polymer is incorporated into the hydrogel, the trend of the transparency increasing with an increase in the concentration of Ad in P(NIPAAm-co-AdAAm) can be attributed to the enhanced immobilization of P(NIPAAm-co-AdAAm) on the hydrogels via host-guest interactions. The phase transition of P(NIPAAm-co-AdAAm), with a larger amount of Ad in the hydrogel, was more strongly restrained because P(NIPAAm-co-AdAAm) was fixed in the network by the formation of a host-guest complex between the Ad group in P(NIPAAm*co*-AdAAm) and  $\beta$ -CD in the hydrogel (Figure 3-4b). The water content of the hydrogels using P(NIPAAm-co-AdAAm) with 1.0, 3.0, 5.0, and 7.0 mol% of AdAAm in feed ratio were 93, 91 89, and 87%, respectively. This result suggests that sufficient amount of water surrounded the thermoresponsive polymers for the phase transition. In the case of the hydrogel with P(NIPAAm<sub>99</sub>-co-AdAAm<sub>1</sub>), the transmittance of the hydrogel itself was quite low, and thus, it was difficult to recognize the pressed area.



**Figure 3-4.** (a) Photographs and transmittance of the hydrogels fabricated using different P(NIPAAm*co*-AdAAm) (1.0, 3.0, 5.0, and 7.0 mol% of AdAAm to that of the total monomers) with a fixed amount of β-CDAAm (5.0 mol% with respect to that of DMAAm). (b) Schematic of the phase transition behaviors of P(NIPAAM<sub>99</sub>-*co*-AdAAm<sub>1</sub>) and P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) under heating. (c) Photographs and transmittance of the hydrogels prepared using different molar ratios of β-CDAAm (15, 30, 45, and 60 mol% with respect to that of Ad) with P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>). ((a, c) Circular and square symbols represent the transmittance before and after compression, respectively. The compression ratio was 70% unless otherwise noted.) (d) Photographs and transmittance of the hydrogels after compression at 30, 50, and 70%. (e) Photographs and signal-to-noise ratio of the hydrogels after compression at 25, 37, and 50 °C. ((d, e) The hydrogel was prepared using P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) with 30 mol% of β-CDAAm to that of Ad.) In all pictures and figures, the observation and measurement were performed at 37 °C.

This is because the amount of Ad was not adequate to suppress the phase transition of P(NIPAAm<sub>99</sub>-co-AdAAm<sub>1</sub>) immobilized in the hydrogel via supramolecular bonding. The mechanical strength of this hydrogel was insufficient to endure 70% compression, as insufficient amount of Ad resulted in the formation of only low numbers of host-guest complexes in the hydrogel. Conversely, owing to the sufficient amount of Ad incorporated in the thermoresponsive polymer, the hydrogel with P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) demonstrated an excellent mechano-responsive behavior with high contrast between the pressed and unpressed areas, owing to the high transparency of the unpressed background. This result supports the fact that the phase transition of P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) was suppressed by the immobilization of the thermoresponsive polymer in the hydrogel via host-guest interactions under heating. On the other hand, the phase transition was caused by the application of mechanical stress, leading to a decrease in the transmittance of the pressed area. Second, the hydrogels fabricated using different molar ratios of  $\beta$ -CDAAm with P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) were evaluated to investigate the effect of  $\beta$ -CD on the transparency of the hydrogels (Figure 3-4c). Considering the results discussed previously, when the amount of β-CD increases, the P(NIPAAm-co-AdAAm) will be immobilized more strongly into the hydrogel; hence, the phase transition will be further restricted, resulting in hydrogels with higher transparency. However, the results obtained upon varying the molar ratio of  $\beta$ -CD indicate that the transmittance decreased with an increase in the amount of  $\beta$ -CD. This turbidity was probably due to an increase in the heterogeneity of the polymer network in the hydrogels caused by the greater number of crosslinking points of the host-guest complex. The mechanical property of the hydrogel with 15 mol% of β-CDAAm to Ad was insufficient to endure 70% compression due to the lack of the host-guest complex, and mechano-responsiveness was also unclear. Therefore, the hydrogel with  $\beta$ -CDAAm at 30 mol% with respect to that of Ad (5.0 mol% with respect to that of DMAAm) was selected as the most suitable one as it showed good mechano-responsive and mechanical properties with a highly transparent background.

#### Effect of the compression condition on the mechano-response

Furthermore, the dependence of the decrease in transmittance on the compression ratio was



**Figure 3-5.** (a) Stress–strain curves of the hydrogel using P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) with 5.0 mol% of  $\beta$ -CDAAm. The black and red dotted lines correspond to the 1st and 2nd compression at 37 °C, respectively. (b) Stress–strain curves of the hydrogel compressed at 25, 37 and 50 °C (blue, black, and red, respectively). (c) Frequency dependence of the storage moduli (G') and loss moduli (G") of the hydrogel at 37 °C.

evaluated to investigate the effect of the degree of dissociation of the host–guest complex on the mechanoresponsive property of the hydrogel. The hydrogel was subjected to 30, 50, and 70% compression, and the corresponding stress was  $0.02 \pm 0.00$ ,  $0.15 \pm 0.01$ , and  $0.87 \pm 0.03$  MPa, respectively (**Figure 3-5a**). From **Figure 3-4d**, it is evident that there was a greater decrease in the transmittance at higher compression ratios. This result suggests that the more the host–guest complexes dissociated under a larger mechanical force, the more P(NIPAAm-*co*-AdAAm) precipitated in the hydrogel,



**Figure 3-6.** Stress–strain curve of the hydrogel using  $P(NIPAAm_{95}-co-AdAAm_5)$  with 5.0 mol% of  $\beta$ -CDAAm in tensile mode.

supporting the fact that the phase transition was driven by the sacrificial dissociation of the host–guest complex in response to the applied stress. In the hydrogel compressed at 50%, the star shape can be recognized only slightly. This result indicates that the minimum threshold of the compression stress for the detection of the mechano-responsive behavior was approximately 0.15 MPa during compression. Certainly, no significant linearity between the change in transmittance and compression ratio/stress was observed, probably because the correlation between the level of the phase transition and the dissociation of the host–guest complex is complicated. However, the decrease in the transmittance highly depended on the compression

ratio. Therefore, the author has concluded that the dissociation of host–guest complex is the main factor for the phase transition that leads to the mechano-responsive property of the hydrogels. Additionally, it should be noted that the hydrogels were broken easily under tensile stress in water at 37 °C (**Figure 3-6**, the breaking stress and breaking strain were  $11 \pm 4$  kPa and  $54 \pm 13\%$ , respectively). This is probably due to weak network structure as seen in typical chemically cross-linked hydrogels. Also, the mechano-responsive behavior was not observed in tensile mainly because the mechanical strength of the hydrogels was insufficient to induce the propagation of the applied stress to supramolecular bonding.

The response time of the mechanoresponsive behavior was analyzed by changing duration between the end of the compression and unloading (**Figure 3-7**). Even when the hydrogel was unloaded instantly after 70% compression, the star shape of the pressed area was able to be recognized, although the pattern was less obvious than those produced under longer



0 s 30 s 60 s 90 s Figure 3-7. The photograph of the hydrogels, using P(NIPAAm<sub>95</sub>-*co*-AdAAm<sub>5</sub>) with 5.0 mol% of β-CDAAm, after 70% compression with the different duration between the end of the compression and unloading (0, 30, 60, and 90 s, respectively).

duration of the compression state of more than 30 s. By maintaining the compression state for longer duration, the pattern of the compression area became more obvious due to the further progress of the dissociation of the host–guest complex.

Moreover, to clarify the effect of the compression temperature on the mechanoresponsiveness, the change in transmittance with respect to the compression temperature was evaluated. It has been reported that the association constant of the host–guest complex of  $\beta$ -CD and Ad in water was almost constant at different temperatures<sup>33</sup>. Therefore, it is expected that the strength of the host–guest interaction itself in the hydrogels did not change significantly in the range of the temperature from 25 °C to 50 °C. **Figure 3-4e** shows that above the LCST, the decrease in transmittance and the signal-to-noise ratio between the pressed and unpressed areas were more significant at higher compression temperatures (37 °C and 50 °C), whereas at temperatures below or around the LCST (the LCST of P(NIPAAm<sub>95</sub>-co-AdAAm<sub>5</sub>) was 23 °C in the absence of  $\beta$ -CD), the transmittance was almost the same before and after compression (25 °C). Therefore, a change occurs in the turbidity of the hydrogel when the following conditions are satisfied: one, the hydrogel is heated sufficiently above the LCST of P(NIPAAm*co*-AdAAm), and two, the hydrogel is compressed. The greater decrease in the transmittance resulting from compression at higher temperatures suggests that this change in the appearance is derived from the phase transition of P(NIPAAm-*co*-AdAAm). This is because hydrophobic interactions, which induce phase transitions, become stronger at higher temperatures.

#### Mechanism and repeatability of the mechano-response

The proposed mechanism of the mechano-responsiveness of the hydrogel is described below (Figure 3-1). Initially, P(NIPAAm-co-AdAAm) in the hydrogel is immobilized via the supramolecular bonding of the host-guest complex at multiple points, below the LCST of P(NIPAAm-co-AdAAm). This largely restricts the phase transition of P(NIPAAm-co-AdAAm), even above the LCST. When mechanical force is applied to the hydrogel by compression, the supramolecular bonding of the host-guest complexes between the hydrogel and P(NIPAAmco-AdAAm) dissociate sacrificially, and simultaneously, the phase transition and aggregation of P(NIPAAm-co-AdAAm) are induced in the hydrogels. After unloading, the aggregation state of the hydrogels is preserved because of the decrease in the LCST of P(NIPAAm-co-AdAAm). This decrease in the LCST is because of the exposure of the hydrophobic Ad group by the dissociation of the supramolecular bonds, resulting in a decrease in the transmittance of the hydrogel. This transition from the metastable state to the stable state is irreversible because the aggregated P(NIPAAm-co-AdAAm) can no longer dissolve at temperatures above the LCST<sup>30</sup>; and therefore, the low transmittance of the stressed area can be maintained after the removal of external stress. Thus, as illustrated in Figure 3-8a-c, it was possible to form a pattern with a complicated shape solely by compression, even with patterns involving thin lines (approximately 300 mm width, shown in Figure 3-8b,c, a hexagon-shaped pattern).

Furthermore, aggregates that have undergone a phase transition due to compression are stable but can be solubilized by cooling to below the LCST. A schematic of the repeatable printing of the hydrogel is shown in **Figure 3-8d**. When the hydrogel was compressed using a



**Figure 3-8.** (a) Schematic of the patterning of the hydrogel using a metal motif. Photographs of (b) the metal motifs with repeating square-shaped (left) and hexagon-shaped (right) holes, and (c) the hydrogels patterned using them with 65% compression at 50 °C. The thickness of the substrates was 0.3 mm. (d) Schematic of the repeatable printing on the mechano-responsive hydrogel. (e) Photograph of the stamps used in the experiment. (f) Photographs of the hydrogels compressed at 70% using a star-, heart-, and square-shaped stamp with a circular hole, which were subsequently cooled at 15 °C for 1 min after each compression.

star-shaped stamp, only the area that was under pressure became turbid, representing significant mechano-responsiveness а (Figure 3-8e,f). Furthermore, when the hydrogel was cooled at 15 °C for 1 min, the white turbid star shape created at 37 °C disappeared from the hydrogel. This is because the precipitated P(NIPAAm-co-AdAAm) dissolved owing to the phase transition below the LCST, and the Ad group of P(NIPAAm-*co*-AdAAm) was included reversibly by β-CD and incorporated in the hydrogel. When the heart-shaped stamp applied was



**Figure 3-9.** Photographs of hydrogels after 70% compression (left) and after 5 days of being stored at 37 °C (right), fabricated using different P(NIPAAm*co*-AdAAm) (1.0, 3.0, 5.0, and 7.0 mol% of AdAAm to the total monomers) with a fixed amount of  $\beta$ -CDAAm (30 mol% to that of Ad, 5.0 mol% to that of DMAAm).

subsequently at the same position, a heart shape was stamped onto the hydrogel once again, demonstrating the viability of repeatable printing on the hydrogel. The mechano-responsive property was also clearly observed when a square-shaped stamp with a circular hole was used. In addition, the appearance of the compressed area was preserved over several days when the compressed hydrogel was maintained at 37 °C, suggesting that the phase transition and precipitation of the thermoresponsive polymer is mainly caused by compression rather than heating (**Figure 3-9**). Moreover, no size change was observed at the macroscopic level over several days. As described, the hydrogel exhibits great mechano-responsive properties for the patterning or printing of various shapes, and the printed shape can be maintained by storing the hydrogel at temperatures above the LCST. In addition, the printed shape can be erased by cooling the hydrogel below the LCST, supporting the controllable reversibility of its mechano-responsive property.

#### **3-4.** Conclusions

In conclusion, the author successfully developed a novel hydrogel demonstrating mechanoresponsive behavior owing to the combination of a thermoresponsive polymer and host–guest interactions. The thermoresponsive polymer immobilized *via* host–guest complex formation in the hydrogel acted as a mechano-responsive component by its force-induced phase transition owing to the dissociation of the host–guest complex, resulting in a decrease in the transmittance of the hydrogel. This phase transition and precipitation of the thermoresponsive polymer were mainly caused by compression rather than heating. The decrease in the transmittance correlated with the level of applied force and temperature at compression. Furthermore, the preservation or deletion of a region that undergoes a change because of mechanical stress could be controlled by maintaining the temperature above the LCST or cooling below the LCST, respectively, thereby demonstrating a controllable reversibility of its mechano-responsiveness. The present concept to create a metastable state of responsive molecules utilizing supramolecular bonding as a flexible molecular switch would contribute to various mechano-responsive systems including stress detection and patterning of materials.

#### **3-5. References**

- 1. H. Izawa, K. Kawakami, M. Sumita, Y. Tateyama, J. P. Hill, K. Ariga, *J. Mater. Chem. B* **2013**, *1*, 2155.
- 2. T. Matsuda, R. Kawakami, R. Namba, T. Nakajima, J. P. Gong, Science 2019, 363, 504.
- D. A. Davis, A. Hamilton, J. Yang, L. D. Cremar, D. V. Gough, S. L. Potisek, M. T. Ong, P. V. Braun, T. J. Martínez, S. R. White, J. S. Moore, N. R. Sottos, *Nature* 2009, 459, 68.
- 4. C. K. Lee, D. A. Davis, S. R. White, J. S. Moore, N. R. Sottos, P. V. Braun, *J. Am. Chem. Soc.* **2010**, *132*, 16107.
- 5. K. Imato, T. Kanehara, T. Ohishi, M. Nishihara, H. Yajima, M. Ito, A. Takahara, H. Otsuka, *ACS Macro Lett.* **2015**, *4*, 1307.
- 6. L. Wang, W. Zhou, Q. Tang, H. Yang, Q. Zhou, X. Zhang, Polymers 2018, 10, 994.
- C. G. Schäfer, M. Gallei, J. T. Zahn, J. Engelhardt, G. P. Hellmann, M. Rehahn, *Chem. Mater.* 2013, 25, 2309.
- 8. R. Kizhakidathazhath. Y. Geng, V. S. R. Jampani, C. Charni, A. Sharma, J. P. F. Lagerwall, *Adv. Funct. Mater.* **2020**, *30*, 1909537.
- 9. Y. Yue, T. Kurokawa, M. A. Haque, T. Nakajima, T. Nonoyama, X. Li, I. Kajiwara, J. P. Gong, *Nat. Commun.* 2014, *5*, 4659.
- 10. G. H. Lee, T. M. Choi, B. Kim, S.H. Han, J. M. Lee, S. H. Kim, ACS Nano 2017, 11, 11350.
- 11. Y. Sagara, T. Kato, Nat Chem. 2009, 1, 605.
- 12. Y. Sagara, M. Karman, E. Verde-Sesto, K. Matsuo, Y. Kim, N. Tamaoki, C. Weder, *J. Am. Chem. Soc.* **2018**, *140*, 1587.
- 13. C. Löwe, C. Weder, Adv. Mater. 2002, 14, 1625.
- 14. A. Lavrenova, D. W. R. Balkenende, Y. Sagara, S. Schrettl, Y. C. Simon, C. Weder, J. Am. Chem. Soc. 2017, 139, 4302.
- 15. A. Harada, Y. Takashima, M. Nakahata, Acc. Chem. Res. 2014, 47, 2128.
- 16. A. Kawamura, T. Kiguchi, T. Nishihata, T. Uragami, T. Miyata, *Chem. Commun.* **2014**, *50*, 11101.
- 17. P. Zhang, X. Qian, Z. Zhang, C. Li, C. Xie, W. Wu, X. Jiang, ACS Appl. Mater. Interfaces 2017, 9, 5768.
- A. Alsbaiee, B. J. Smith, L. Xiao, Y. Ling, D. E. Helbling, W. R. Dichtel, *Nature* 2016, 529, 190.
- 19. S. Mizuno, T. Asoh, Y. Takashima, A. Harada, H. Uyama, Chem. Commun. 2020, 56, 14408.
- 20. G. Zhang, Y. Luan, X. Han, Y. Wang, X. Wen, C. Ding, J. Gao, *Green Chem.* 2013, 15, 2081.
- 21. A. Sugawara, T. Asoh, Y. Takashima, A. Harada, H. Uyama, *Polym. Degrad. Stab.* **2020**, *177*, 109157.
- 22. T. Kakuta, Y. Takashima, A. Harada, Macromolecules 2013, 46, 4575.
- 23. A. Halperin, M. Kröger, F. M. Winnik, Angew. Chem. Int. Ed. 2015, 54,15342.
- 24. T. Tanaka, E. Sato, Y. Hirokawa, S. Hirotsu, J. Peetermans, Phys. Rev. Lett. 1985, 55, 2455.

- 25. Y. S. Kim, M. Liu, Y. Ishida, Y. Ebina, M. Osada, T. Sasaki, T. Hikima, M. Takata, T. Aida, *Nat. Mater.* **2015**, *14*, 1002.
- 26. S. Maeda, Y. Hara, T. Sakai, R. Yoshida, S. Hashimoto, Adv. Mater. 2007, 19, 3480.
- 27. H. Feil, Y. H. Bae, J. Feijen, S. W. Kim, Macromolecules 1993, 26, 2496.
- 28. Y. G. Takei, T. Aoki, K. Sanui, N. Ogata, T. Okano, Y. Sakurai, *Bioconjugate Chem.* **1993**, *4*, 341.
- 29. H. Y. Liu, X. X. Zhu, Polymer 1999, 40, 6985.
- 30. S. Schmitz, H. Ritter, Angew. Chem. Int. Ed. 2005, 44, 5658.
- 31. O. Kretschmann, S. W. Choi, M. Miyauchi, I. Tomatsu, A. Harada, H. Ritter, *Angew. Chem. Int. Ed.* **2006**, *45*, 4361.
- 32. M. Miyauchi, A. Harada, J. Am. Chem. Soc. 2004, 126, 11418.
- 33. K. Leko, M. Hanževački, Z. Brkljača, K. Pičuljan, R. Ribić, J. Požar, *Chem. Eur. J.* **2020**, 26, 5208.

## **Concluding remarks**

In this doctoral thesis, the mechanical response of hydrogels functionalized using hostguest interaction between  $\beta$ -CD and Ad as sacrificial bonds was investigated. Incorporation of the supramolecular bond enhanced the mechanical strength and toughness of the composite hydrogels. Moreover, the sacrificial bonds were able to act as a molecular switch of the mechano-responsive hydrogels.

In chapter 1, cellulose fiber-based composite hydrogels, in which host–guest interaction between  $\beta$ -CD and Ad was incorporated at the filler/ matrix interface, were fabricated. Admodified supramolecular cellulose nanofiber exhibited higher dispersibility in response to the addition of  $\beta$ -CD, indicating the formation of the inclusion complex at the surface of the fiber. Great interfacial compatibility, by incorporation of the supramolecular bonding between cellulose fiber and the matrix, was achieved by *in situ* preparation of the matrix, in the presence of the filler. In the hydrogels, the supramolecular filler acted as the multi-physical cross-linking points. Significant enhancement of the mechanical strength of the hydrogels indicates the interfacial host–guest complex transferred external stress from the matrix to the filler effectively. In addition, improvement in toughness resulted from the sacrificial cleavage of the host–guest complex that dissipated mechanical energy when the hydrogels were highly deformed.

In chapter 2, PNIPAAm-based thermoresponsive composite hydrogels reinforced with supramolecular filler were prepared. At swelling states below the LCST, interfacial supramolecular bonding acted as physical cross-links, leading to the increase in the maximum stress of the hydrogels. Additionally, the toughness of the hydrogels was also improved, owing to energy dissipation resulting from the sacrificial dissociation of the host–guest complex under applied stress. Furthermore, even when the hydrogels had shrunk above their LCST, the host–guest interaction was still maintained as physical cross-linking points. This led to superior maximum stress and elongation at break of the deswollen hydrogels compared to hydrogels without host–guest interactions. The host–guest interactions at the filler/matrix interface contributed to improvements in the mechanical properties of the hydrogels, both in the swelling and deswelling states.

In chapter 3, novel hydrogels demonstrating mechano-responsive behavior through the combination of a thermoresponsive polymer and host–guest interaction were developed. The thermoresponsive polymer immobilized *via* host–guest complex formation between  $\beta$ -CD and Ad in the hydrogel acted as a mechano-responsive component by its force-induced phase transition, owing to the dissociation of the host–guest complex as a molecular switch. The fabricated hydrogels demonstrated mechano-responsive behavior, such as an increase in the turbidity of the hydrogel. This behavior correlated with the level of applied force and temperature at compression, indicating dissociation of the host–guest complex and phase transition of the thermoresponsive polymer, respectively. Furthermore, the preservation or deletion of a region that undergoes a change due to mechanical stress could be controlled by maintaining the temperature above the LCST or cooling below the LCST, respectively, thereby demonstrating a controllable reversibility of its mechano-responsiveness.

In conclusion, the author developed strategies to functionalize hydrogels using host–guest inclusion complex between  $\beta$ -CD and Ad. The formation, and sacrificial dissociation of the inclusion complex induced by external stress, played roles in the demonstration of the mechanical responsive properties of the hydrogels, in terms of enhancement of the mechanical strength and toughness of the composite materials. In addition, the host–guest complex acted as a mechanical switch for the expression of the mechano-responsive change in the appearance of the hydrogel. The author believes that this material design will contribute to the development of functional soft materials in the next generation, applications and technology for guaranteed safety in the usage of materials.

# **List of Publications**

1. Composite Hydrogels Reinforced by Cellulose-based Supramolecular Filler

Akihide Sugawara, Taka-Aki Asoh\*, Yoshinori Takashima, Akira Harada, and Hiroshi Uyama\*

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2. Thermoresponsive Hydrogels Reinforced with Supramolecular Cellulose Filler
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3. Mechano-Responsive Hydrogels Driven by the Dissociation of a Host–Guest Complex Akihide Sugawara, Taka-Aki Asoh\*, Yoshinori Takashima, Akira Harada, and Hiroshi Uyama\* *ACS Macro Letters*, **2021**, *10* (7), 971–977. DOI: 10.1021/acsmacrolett.1c00357

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