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Self-Healing, Expansion–Contraction, and Shape-Memory Properties of a Preorganized Supramolecular Hydrogel through Host–Guest Interactions**

*Kohei Miyamae, Masaki Nakahata, Yoshinori Takashima, and Akira Harada**

Abstract: *Supramolecular materials cross-linked between polymer chains by noncovalent bonds have the potential to provide dynamic functions that are not produced by covalently cross-linked polymeric materials. We focused on the formation of supramolecular polymeric materials through host–guest interactions: a powerful method for the creation of nonconventional materials. We employed two different kinds of host–guest inclusion complexes of β-cyclodextrin (βCD) with adamantane (Ad) and ferrocene (Fc) to bind polymers together to form a supramolecular hydrogel (βCD-Ad-Fc gel). The βCD-Ad-Fc gel showed self-healing ability when damaged and responded to redox stimuli by expansion or contraction. Moreover, the βCD-Ad-Fc gel showed a redox-responsive shape-morphing effect. We thus succeeded in deriving three functions from the introduction of two kinds of functional units into a supramolecular material.*

Functional biomolecules and their assemblies form high-order structures in a hierarchical way.[1] These sophisticated structures perform various functions to keep our body in working order; for example, they are involved in the formation of various types of body tissue, recovery from injuries, and expansion–contraction motion to produce mechanical work. These functions in biological systems have been role models for the development of functional materials.[2,3] Molecular recognition is a key concept in the design of such materials,[4] and many examples of supramolecular materials created by a combination of supramolecular and polymer chemistry have been reported so far, such as stimuli-responsive materials,[5–9] self-healing materials,[10–17] artificial muscles and actuators,[18–26] and shape-memory materials.[27–32] More recently, research fields on multistimuli-responsive[33–35] and multifunctional[36] polymers have emerged. We believe that the development of polymeric materials containing two or more kinds of recognition moieties is an elegant approach to supramolecular materials with various functions.

We have reported a number of supramolecular materials, such as macroscopic self-assemblies,[37,38] self-healing materials,[39,40] and artificial muscles,[41,42] based on host–guest interactions between cyclodextrins (CD) and various guest moieties on polymer side chains. However, the single biological-like functions performed in previous studies were still far simpler than those in living organisms, in which many complex biological tissues perform numerous functions. We hypothesized that the introduction of two kinds of functional groups into a polymer would provide more than three functionalities in response to external stimuli. Host–guest complexes serve as substitutes for conventional chemical cross-linkers to enable the synthesis of multitasking materials with self-healing, creep-recovery, and expansion–contraction properties. In particular, if ON/OFF switching is introduced, the resulting reversible host–guest complexation is expected to enable the creation of a shape-morphing material through erasing and writing by external stimuli.

Herein, we report a novel supramolecular hydrogel containing two different kinds of guest moieties with different functional properties (Figure 1a). We utilize two kinds of host–guest inclusion complexes to bind polymers together. One is an inclusion complex between β-cyclodextrin (βCD) and adamantane (Ad), which form a stable inclusion complex with an association constant (K) of $35\times10^3\,\text{M}^{-1}$.[43] The other is an inclusion complex between βCD and ferrocene (Fc). βCD and Fc in its reduced state form a relatively stable inclusion complex with a K value of $17\times10^3\,\text{M}^{-1}$.[44,45] The reduced form of Fc can be included in the cavity, whereas the oxidized form cannot be included owing to its hydrophilic nature. Redox stimuli can control the formation of inclusion complexes between βCD and Fc.[46] Chemical hydrogels bearing βCD and Fc moieties can change their size in response to redox stimuli, and this feature has been utilized in a redox-responsive actuator.[42] In this study, we developed hydrogels bearing two different types of noncovalent cross-links to create hydrogel self-healing, expansion–contraction, and shape-memory properties.

Figure 1b shows the chemical structure of the host–guest gel (βCD-Ad-Fc gel) used in this study. Poly(acrylamide) (pAAm) and poly(N-isopropylacrylamide) (pNIPAAm) were selected as main chains to form the gel. The gel was prepared by conventional free-radical copolymerization after solubilization of the hydrophobic guest monomers by the host monomer βCD–AAm (see Scheme S1 in the Supporting Information). First of all, βCD–AAm and the guest mono-

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[*] K. Miyamae, Dr. M. Nakahata, Dr. Y. Takashima, Prof. Dr. A. Harada
Department of Macromolecular Science
Graduate School of Science, Osaka University
Toyonaka, Osaka, 560–0043 (Japan)
E-mail: harada@chem.sci.osaka-u.ac.jp

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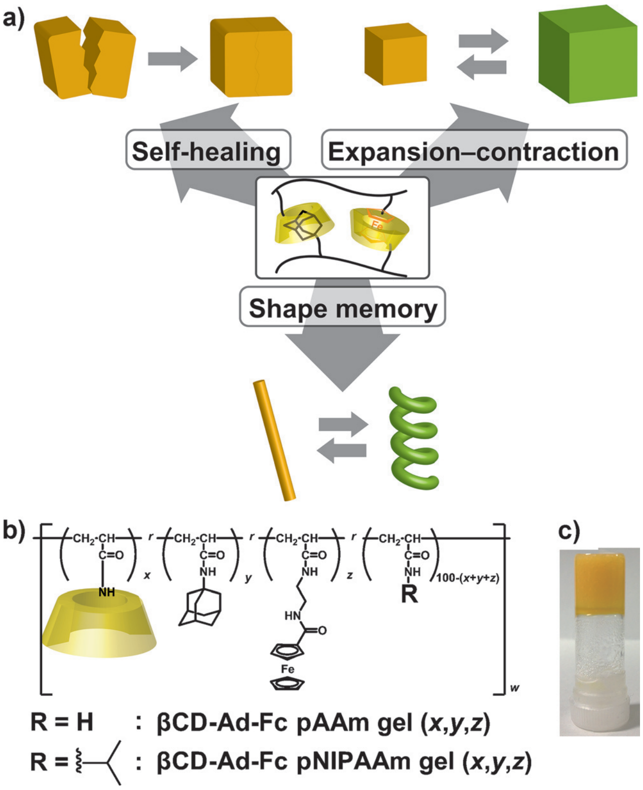

Figure 1. a) Properties of the designed supramolecular polymeric hydrogel with two kinds of noncovalent cross-links (βCD-Ad and βCD-Fc): self-healing, expansion–contraction, and shape memory. b) Chemical structure of the βCD-Ad-Fc gels; *x*, *y*, and *z* indicate the amount (mol%) of βCD-AAm, Ad-AAm, and Fc-AAm units. c) Photograph of the βCD-Ad-Fc pAAm gel (6,3,3).

mers Ad–AAm and Fc–AAm were mixed in a solvent mixture composed of water and DMSO (95:5, v/v). Heating of this turbid suspension resulted in a transparent solution. After this solubilization step, the main-chain monomer and water-soluble radical initiator VA-044 were added, and the mixture was purged with argon and polymerized to give a gel (Figure 1c). The gel was washed thoroughly with DMSO and water to remove unreacted compounds and non-cross-linked polymers. The gels were characterized by ^{1}H solid-state field-gradient magic-angle-spinning (FGMAS) NMR spectroscopy and FTIR spectroscopy (see Figures S1–S3).

Stress–strain measurements were used to investigate the mechanical properties of the βCD-Ad-Fc pAAm gel and the βCD-Ad-Fc pNIPAAm gel. A cuboid gel piece was pulled toward opposite sides by the use of a creepmeter. The initial slope of the linear region of the resulting stress–strain curves (see Figure S6a,b for the stress–strain curves of βCD-Ad-Fc pAAm gels (2,1,1), (3,1.5,1.5), and (6,3,3) and βCD-Ad-Fc pNIPAAm gels (4,2,2), (6,3,3), (8,4,4), and (10,5,5)) corresponded to the Young modulus (E), which is in proportional to cross-linking density. The introduction of more βCD-Ad and βCD-Fc moieties resulted in a larger rupture stress, a larger E value, and a smaller rupture strain owing to the formation of noncovalent cross-linking points. Competitive experiments (see Figures S8 and S9) also supported the existence of host–guest interactions within the gel. These results indicate that host–guest complexes inside βCD-Ad-Fc gels effectively function as cross-linking points, like chemical cross-linkers.

We investigated the self-healing properties resulting from the reversible noncovalent cross-links inside the gels. A cubic piece of βCD-Ad-Fc pNIPAAm gel (6,3,3) ($4\times4\times4$ mm^3) was cut in half with a razor edge, and the two halves were then reattached to one another. After 3 h under wet conditions, the separated gel pieces had adhered again to form one gel (Figure 2a). Reference gels without Ad and Fc moieties (βCD pNIPAAm gel), without βCD moieties (Fc-Ad gel), and without βCD, Ad, and Fc moieties (pNIPAAm gel) did not show the self-healing property (see Figure S10). Competitive molecules inhibited this self-healing property. When an aqueous solution of sodium adamantanecarboxylate (AdCANa; 100 mM, 0.01 mL) was applied to one of the cut surfaces, no healing was observed when the two cut surfaces were held together for 3 h (Figure 2b). This result indicates that the self-healing between cut surfaces is due to the reformation of host–guest inclusion complexes.

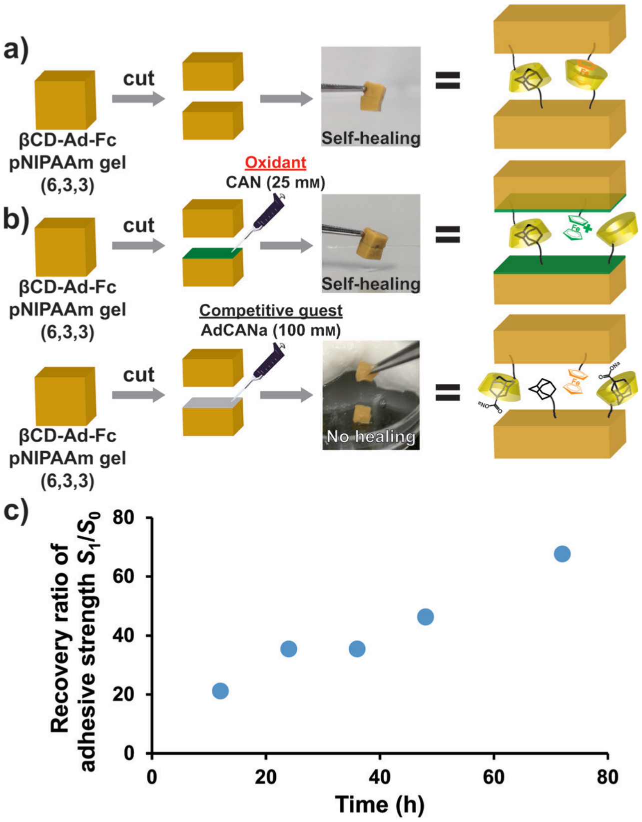

Figure 2. Self-healing of the βCD-Ad-Fc pNIPAAm gel. a) A $4\times4\times4$ mm^3 cubic piece of βCD-Ad-Fc pNIPAAm gel (6,3,3) was cut in half with a razor edge, and the two cut edges were held together again. Within 2 h under wet conditions, the gel pieces adhered to form one gel. b) When an aqueous solution of the oxidizing agent CAN (25 mM, 0.01 mL) was applied to one of the cut surfaces, healing was observed after 2 h. When an aqueous solution of AdCANa (100 mM, 0.01 mL) was applied to one of the cut surfaces, no healing was observed. c) Recovery-time dependency of the stress–recovery ratio for βCD-Ad-Fc pNIPAAm gel (10,5,5).

Self-healing was observed even in the presence of an oxidizing agent. An aqueous solution of the oxidizing agent ammonium cerium nitrate (CAN; 25 mM, 0.01 mL) was applied to one of the cut surfaces. βCD shows a high affinity for the reduced state of the Fc group because of its hydrophobic nature. When the Fc moiety is oxidized, the oxidized ferrocenium cation (Fc^+) is too hydrophilic to be included in the cavity of βCD. Even under these conditions, self-healing was observed after 3 h (Figure 2b).

The efficiency of the self-healing was estimated quantitatively by stress–strain measurements (see Figure S11a for stress–strain curves of the original βCD-Ad-Fc pNIPAAm gel (6,3,3) and the same gel after it had been cut and the pieces reconnected over a period of 24 h). The recovery ratio of the adhesive strength depended on the amount of βCD-Ad-Fc moieties present and the recovery time, and increased to 68% in the case of the βCD-Ad-Fc pNIPAAm gel (10,5,5) with a healing time of 72 h (Figure 2c; see also Figure S11b). The healing efficiency was significantly decreased by the addition of a competitive molecule or an oxidizing agent to the cut surface (see Figure S12 for the rupture stress of the original gel, the healed gel, the healed gel applied with CAN, and the gel applied with the competitive guest AdCANa). These results indicate that both βCD–Fc and βCD–Ad contribute to self-healing (see Figures S7, S13, and S14).

We regulated the expansion–contraction property of the βCD-Ad-Fc gels by using redox reagents. A 1 × 1 × 1 mm^3 cube of the βCD-Ad-Fc pAAm gel (2,1,1) was immersed in 0.1M Tris/HCl buffer (pH 7) before the redox reactions. Tris/HCl buffer with a high ionic strength suitably controls the cross-link density of the βCD-Ad-Fc gels by eliminating the electric repulsion between the Fc^+ units. The following experimental procedure was used: The βCD-Ad-Fc pAAm gel immersed in Tris/HCl buffer (0.1M) was placed in Tris/HCl buffer containing CAN (25 mM). After standing for 2 h, the oxidized βCD-Ad-Fc gel was immersed in the original Tris/HCl buffer again. Figure 3a shows photographs of βCD-Ad-Fc pAAm gel (2,1,1) before and after oxidation. The redox reaction of the Fc moiety inside the gel was monitored by UV/Vis spectroscopy (see Figures S4 and S5). Oxidation with CAN increased the length of the gel, whereas continuous reduction of the gel restored the initial length (Figure 3b; see also Figure S16). In contrast, βCD-Ad gel (2,1) and pAAm gel (1) as reference gels did not exhibit expansion behavior in response to CAN (see Figure S15). Fc^+ exhibited low affinity for βCD owing to its cationic nature, which resulted in dissociation of the βCD–Fc inclusion complex. Dissociation of the inclusion complex between βCD and Fc decreases the cross-link density to swell the gel. However, after reduction, the inclusion complex reforms to increase the cross-link density and shrink the gel. The change in the cross-link density in response to the redox stimuli led to the uptake and release of water from the gel, thus altering the volume of the βCD-Ad-Fc gel (Figure 3c).

Finally, we controlled the material shape of the supramolecular hydrogel through switching of the reversible bond formation. Figure 4a shows the writing procedure for a helical shape. First, a rod-shaped sample of βCD-Ad-Fc pAAm gel (2,1,1) (diameter: 5 mm, length: 50 mm) was immersed in a buffer containing 25 mM CAN to fix it into a helical shape. Subsequently, the gel was immersed in the original buffer. The helical-rod gel was then taken from the sample tube and put in the buffer without any external stress for 3 days. The released gel retained its helical shape. This shape-memory effect did not occur without the oxidation–reduction cycle. The oxidation of the Fc moieties and their exclusion from the cavity of βCD to generate free βCD facilitates exchange of the βCD–Ad inclusion complex under the mechanical stress. Upon reduction, the Fc moieties reform inclusion complexes with βCD at other positions in the gel (Figure 4b). Control of the two kinds of noncovalent cross-links by redox stimuli led to the fixation of the temporary shape of the gel.

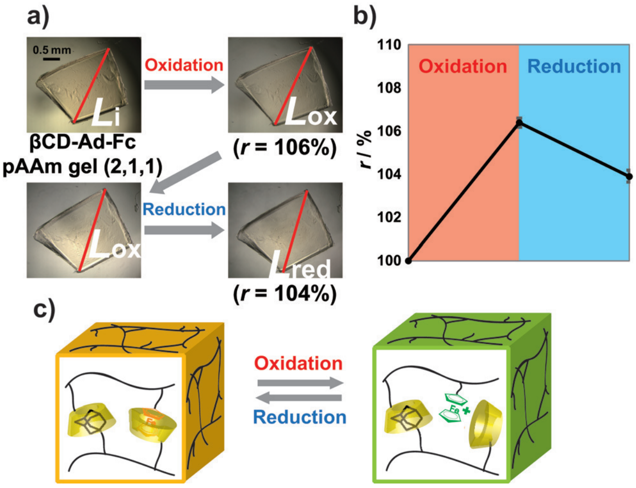

Figure 3. Expansion–contraction of the βCD-Ad-Fc gel in response to redox stimuli. a) Photographs of βCD-Ad-Fc pAAm gel (2,1,1) soon after immersion in Tris/HCl buffer with CAN (25 mM; left) and after 2 h (right). Red lines indicate the measured distance ("length") in the gel. Scale bar indicates 0.5 mm. b) Relative length ratio (*r*) of βCD-Ad-Fc pAAm gel (2,1,1) before and after oxidation, and after subsequent reduction. c) Schematic illustration of the redox-responsive expansion–contraction of the βCD-Ad-Fc gel.

In conclusion, we successfully developed a supramolecular hydrogel capable of self-healing, expansion–contraction, and shape memory in response to redox stimuli. All these features are based on selective molecular recognition between βCD and two kinds of guest moieties, Ad and Fc. The reversible nature of the host–guest complexation gives the gel the property of self-healing, and the redox-responsiveness of βCD–Fc enables the contraction and expansion of the gel. The combination of two different types of cross-links unexpectedly gave the hydrogel the property of shape memory regulated by redox stimuli. Such supramolecular hydrogels with various functions are expected to be the next generation of intelligent soft materials, with properties that more closely resemble those of biological systems.

Experimental Section

Preparation of the gels: βCD-AAm, Ad-AAm, Fc-AAm, methylenebis(acrylamide) (MBAAm), and AAm were polymerized by radical copolymerization initiated by VA-044 in the mixed solvent

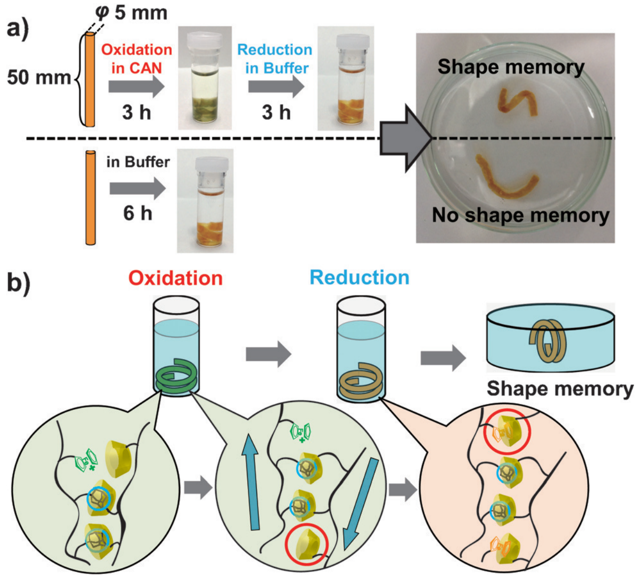

Figure 4. Shape-change experiment with the βCD-Ad-Fc pAAm gel. a) Experimental procedure. First, a linear-cylindrical piece of βCD-Ad-Fc pAAm gel (2,1,1) (φ: 5 mm, length: 50 mm) was oxidized in an aqueous buffer containing CAN (25 mM) for 3 h, during which time it adopted a helical shape. Subsequently, the gel was reduced by immersion in the original buffer. When the gel was shaken in the buffer for 3 days, it retained its helical shape. This shape-memory effect did not occur without the oxidation–reduction cycle. b) Schematic illustration of the shape-memory mechanism.

water/DMSO (95:5, v/v; see Schemes S1–S4 in the Supporting Information).

Keywords: artificial muscles · host–guest systems · self-healing · shape memory · supramolecular gels

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[1] “Muscles”: *Comparative Anatomy of the Vertebrates*, 7th ed. (Eds.: G. C. Kent), chap. 11, Wm. C. Brown Publishers, Dubuque, IA, **1987**, pp. 326–374.
[2] A. Coskun, M. Banaszak, R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.* **2012**, *41*, 19–30.
[3] *Smart Materials and Structures* (Eds.: M. V. Gandhi, B. S. Thompson), Chapman & Hall, London, **1992**.
[4] T. Aida, E. W. Meijer, S. I. Stupp, *Science* **2012**, *335*, 813–817.
[5] *Handbook of Stimuli-Responsive Materials* (Ed.: W. U. Marek), Wiley-VCH, Weinheim, **2011**.
[6] *Responsive Polymer Materials: Design and Applications* (Ed.: S. Minko), Blackwell, Oxford, **2006**.
[7] T. Ikeda, O. Tsutsumi, *Science* **1995**, *268*, 1873–1875.
[8] Y. Yu, M. Nakano, T. Ikeda, *Nature* **2003**, *425*, 145–145.
[9] M. Irie, T. Fukaminato, K. Matsuda, S. Kobatake, *Chem. Rev.* **2014**, *114*, 12174–12277.
[10] *Self-Healing Polymers: From Principles to Applications* (Ed.: W. H. Binder), Wiley-VCH, Weinheim, **2013**.
[11] Y. Yang, M. W. Urban, *Chem. Soc. Rev.* **2013**, *42*, 7446–7467.
[12] S. R. White, N. R. Sottos, P. H. Geubelle, J. S. Moore, M. R. Kessler, S. R. Sriram, E. N. Brown, S. Viswanathan, *Nature* **2001**, *409*, 794–797.
[13] S. D. Bergman, F. Wudl, *J. Mater. Chem.* **2008**, *18*, 41–62.
[14] P. Cordier, F. Tournilhac, C. Soulie-Ziakovic, L. Leibler, *Nature* **2008**, *451*, 977–980.
[15] B. Ghosh, M. W. Urban, *Science* **2009**, *323*, 1458–1460.
[16] Q. Wang, J. L. Mynar, M. Yoshida, E. Lee, M. Lee, K. Okuro, K. Kinbara, T. Aida, *Nature* **2010**, *463*, 339–343.
[17] M. Burnworth, L. Tang, J. R. Kumpfer, A. J. Duncan, F. L. Beyer, G. L. Fiore, S. J. Rowan, C. Weder, *Nature* **2011**, *472*, 334–337.
[18] Y. Osada, H. Okuzaki, H. Hori, *Nature* **1992**, *355*, 242–244.
[19] C. Ohm, M. Brehmer, R. Zentel, *Adv. Mater.* **2010**, *22*, 3366–3387.
[20] M. Shahinpoor, K. J. Kim, *Smart Mater. Struct.* **2005**, *14*, 197–214.
[21] T. F. Otero, M. T. Cortés, *Adv. Mater.* **2003**, *15*, 279–282.
[22] H.-J. Schneider, K. Kato, R. Strongin, *Sensors* **2007**, *7*, 1578–1611.
[23] H.-J. Schneider, R. M. Strongin, *Acc. Chem. Res.* **2009**, *42*, 1489–1500.
[24] H.-J. Schneider, K. Kato, *J. Mater. Chem.* **2009**, *19*, 569–573.
[25] *Electroactive Polymer (EAP) Actuators as Artificial Muscles—Reality, Potential and Challenges*, 2nd ed. (Ed.: Y. Bar-Cohen), SPIE Press, Bellingham, **2004**.
[26] *Conductive Electroactive Polymers: Intelligent Materials Systems*, 2nd ed. (Eds.:G. G. Wallace, P. R. Teasdale, G. M. Spinks, L. A. P. Kane-Maguire), CRC, Boca Raton, **2002**.
[27] Y. Osada, A. Matsuda, *Nature* **1995**, *376*, 219–219.
[28] a) A. Lendlein, S. Kelch, *Angew. Chem. Int. Ed.* **2002**, *41*, 2034–2057; *Angew. Chem.* **2002**, *114*, 2138–2162; b) A. Lendlein, H. Jiang, O. Junger, R. Langer, *Nature* **2005**, *434*, 879–882.
[29] H. Koerner, G. Price, N. A. Pearce, M. Alexander, R. A. Vaia, *Nat. Mater.* **2004**, *3*, 115–120.
[30] H. Meng, H. Mohamadian, M. Stubblefield, D. Jerro, S. Ibekwe, S.-S. Pang, G. Li, *Smart Mater. Struct.* **2013**, *22*, 093001.
[31] J. R. Kumpfer, S. J. Rowan, *J. Am. Chem. Soc.* **2011**, *133*, 12866–12874.
[32] Special Issue: Shape Memory and Shape Morphing Polymers (Ed.: C. Bowman), *Polymer* **2014**, *55*, 5847–6196.
[33] R. Cheng, F. Meng, C. Deng, H.-A. Klok, Z. Zhong, *Biomaterials* **2013**, *34*, 3647–3657.
[34] J. Zhuang, M. R. Gordon, J. Ventura, L. Li, S. Thayumanavan, *Chem. Soc. Rev.* **2013**, *42*, 7421–7435.
[35] P. Schattling, F. D. Jochum, P. Theato, *Polym. Chem.* **2014**, *5*, 25.
[36] Special Issue: Supramolecular Polymers, *Chem. Soc. Rev.* **2012**, *18*, 5869–6216.
[37] A. Harada, R. Kobayashi, Y. Takashima, A. Hashidzume, H. Yamaguchi, *Nat. Chem.* **2011**, *3*, 34–37.
[38] A. Harada, Y. Takashima, M. Nakahata, *Acc. Chem. Res.* **2014**, *47*, 2128–2140.
[39] M. Nakahata, Y. Takashima, H. Yamaguchi, A. Harada, *Nat. Commun.* **2011**, *2*, 511.
[40] T. Kakuta, Y. Takashima, M. Nakahata, M. Otsubo, H. Yamaguchi, A. Harada, *Adv. Mater.* **2013**, *25*, 2849–2853.
[41] Y. Takashima, S. Hatanaka, M. Otsubo, M. Nakahata, T. Kakuta, A. Hashidzume, H. Yamaguchi, A. Harada, *Nat. Commun.* **2012**, *3*, 1270.
[42] M. Nakahata, Y. Takashima, A. Hashidzume, A. Harada, *Angew. Chem. Int. Ed.* **2013**, *52*, 5731–5735; *Angew. Chem.* **2013**, *125*, 5843–5847.
[43] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875–1918.
[44] A. Harada, S. Takahashi, *J. Inclusion Phenom.* **1984**, *2*, 791–798.
[45] J.-S. Wu, K. Toda, A. Tanaka, I. Sanemasa, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1615–1618.
[46] A. U. Moozyckine, J. L. Bookham, M. E. Deary, D. M. Davies, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1858–1862.
[47] T. Kakuta, Y. Takashima, A. Harada, *Macromolecules* **2013**, *46*, 4575–4579.

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