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First Thermally Responsive Supramolecular Polymer Based on Glycosylated Amino Acid

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Supramolecular chemistry has produced many self-assembled architectures through the elegant control of molecular interactions.[1] In materials science, for instance, rational engineering of crystal lattices successfully leads to zeolite-like catalysts and novel electric or magnetic devices.[2] The controlled arrangement of multiple hydrogen bonding results in new types of liquid crystals[3] and organogels.[4] Recently, advanced supramolecular polymers, in which monomers are noncovalently connected, are expected to be highly advantageous over traditional polymers because of their tunable and recyclable characteristics.[5] In addition to the structural features, dynamic properties in response to an environmental change should be introduced for the sophisticated new materials. Such materials, however, are very rare even in the conventional polymers.[6] We now report the first supramolecular polymer with thermal response. Some glycosylated amino acid derivatives screened by a module combination method form macroscopic hydrogels that reversibly swell or shrink in response to temperature. Structural analysis demonstrated that well-developed hydrogen-bonding networks like native proteins assisted by hydrophobic cores enhanced the thermal stability of the self-assembled fibers. On the basis of these unique features, the present supramolecular polymers were successfully utilized as a carrier matrix for the thermally controlled release of DNA and as an environmentally benign absorbent for the effective removal of water pollutants such as bisphenol A.

The random and/or combinatorial screening of functional materials is now an alternative methodology to rational design. To apply this concept to supramolecular materials science, we recently developed a new solid phase (glyco)lipid synthesis (SPLS).[7,8] During our research, some of the artificial glycolipids were accidentally found to be small-molecule gelators of organic solvents.[7b] More interestingly, an *N*-acetyl-galactosamine-appended amino acid (GalNAc-aa) derivative (**5d**) forms a hydrogel that has potential application in cosmetics, food, biomaterials, and pharmaceuticals.[7c] To explore improved hydrogelators based on the glycosylated amino acid scaffold, the SPLS was improved as shown in Figure 1.

The hydrogelation capability of the obtained small library of GalNAc-aa was roughly screened by the reverse displacement of test tubes containing aqueous solutions of the corresponding GalNAc-aa, indicating that some of them are good hydrogelators (see Figure 1). During measurement of the melting temperature of the hydrogel **5k**, we noticed a remarkable shrinkage by heating while expelling water instead of the typical gel−sol transition. Surprisingly, the shrunken gel swells again by cooling so that the clear macroscopic hydrogel re-forms again (Figure 2). This cycle can be reversibly repeated many times. It is clear that, regardless of being a nonpolymeric small molecule, the GalNAc-aa-based hydrogelator uniquely shows a thermally responsive phase transition which is comparable to the cross-linked poly-*N*-isopropyl-acrylamide (poly-NIPAM).

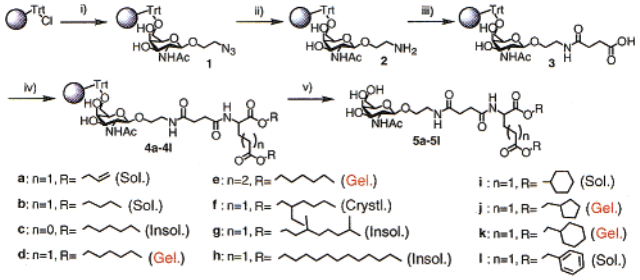

Figure 1. Synthetic scheme and gelation ability of GalNAc-aa.[9]

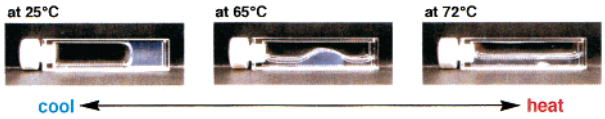

Figure 2. Direct observation of the thermally induced phase transition of the hydrogel of **5k**. Water molecules which are immobilized in the gel matrix at room temperature are partially expelled at 65 °C so that the liquid water and the partially shrunken gel are observed. At 72 °C, the polymer completely shrank to become a white precipitate and more than 99% of water was expelled. [**5k**] = 4 mM in 250 mM NaCl aqueous.

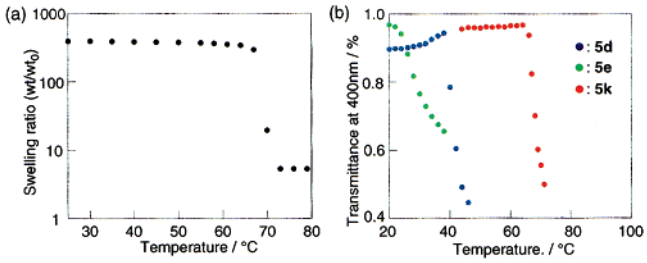

Figure 3. (a) Temperature dependence of the swelling degree of the hydrogel **5k**. (b) A plot of transmittance at 400 nm versus temperature. [GalNAc-aa] = 4 mM in H_2O.

We next investigated the temperature-induced phase transition diagram of the hydrogel **5k** by estimating the released water upon gel shrinkage. The temperature dependence of the swelling degree of **5k** is shown in Figure 3a. The phase transition is clearly discontinuous, and the volume gap reached more than 100-fold over a narrow temperature range (phase transition temperature: *Tp* at 69 °C). When the gel shrinks, the resultant refractive index of the gel increases. This process can be monitored by the transmittance

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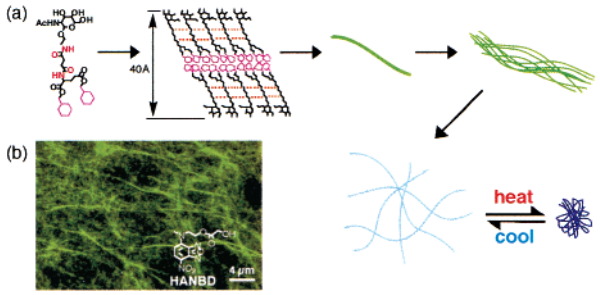

Figure 4. (a) A schematic representation of the hierarchal molecular structures. (b) A confocal laser scanning micrograph of hydrogel **5k**.

change in the gel (Figure 3b). Consistent with the discontinuous phase transition, the turbidity dramatically increases around the *Tp*. Repeated cycling of the temperature induces swelling and shrinking of the hydrogel, and, as a result, the turbidity reversibly decreases and increases, respectively. The phase transition behavior is significantly sensitive to the molecular structure of GalNAc-aa. The *Tp* of **5d** (40 °C) having linear hydrophobic (*n*-hexyl) tails is lower than that of **5k**. The shorter tail renders **5b** to undergo a simple dissolution, and not form a hydrogel. On the other hand, the hydrogel **5j** bearing cyclopentylmethyl groups does not shrink by elevating the temperature, but, instead, simply displays the conventional gel−sol transition at 49 °C. In addition to the hydrophobic tail, the connector part also affects the phase transition behavior. The aminoadipate type of gelator **5e** shows a rather gentle phase transition around 30 °C. The GalNAc-aa **5c** containing an aspartate type of connector is insoluble even in hot water. This slight structural modification enables one to fine-tune the *Tp* in the range between 30 and 70 °C.

Well-developed fibrous networks are observed by a TEM analysis[9] of the hydrogel **5k**, indicating that the noncovalent (i.e., supramolecular) self-assembly of the small molecule forms into fibers, which are physically cross-linked to each other. The powder X-ray diffraction[9] of the xerogel suggested a long spacing of 3.8 nm, which fits into the tilted bimolecular length of **5k**. Another clear peak of 0.4 nm was observed in the wide-angle range, the value of which fits the thickness of the cyclohexyl ring. These data support highly ordered molecular packing based on the bimolecular unit of **5k**. From the FT-IR measurement of the swelled state of **5k**, a significantly shifted stretching band (1615 cm^{-1}) due to the amide carbonyl mainly appeared. That is characteristic of the well-developed hydrogen bond of amides in the protein β-sheet[10] which remains even in the shrunken state. In the case of **5j** exhibiting the conventional gel−sol transition, on the other hand, the corresponding peak in the gel state (1622 cm^{-1}) changed to the more loosely connected carbonyl stretching (1630 cm^{-1}) in the sol state. The nongelator **5b** simply showed an IR band at 1630 cm^{-1}. An environmentally sensitive fluorescent probe, HANBD, which is mixed with **5k** in aqueous solution, strongly emits a green fluorescence at 515 nm even in the swelled hydrogel.[9] By using a confocal laser scanning microscope, the hydrophobic domains stained by HANBD exhibit a brighter contrast than the water phase, and these continuously developed into gel fibers (Figure 4b). Many bundles of these fibers formed into 3D networks with diameters of 0.2−0.6 μm, the values of which are more than 50-fold greater than that observed by TEM. These results suggest that the robust hydrogen-bonding networks assisted by the hydrophobic packing

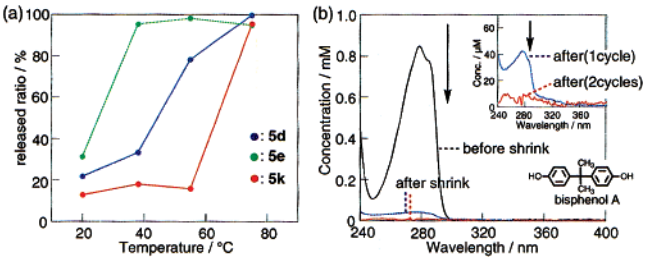

Figure 5. (a) Plots of released ratio of DNA versus temperature for the corresponding hydrogels (**5d**, **5e**, **5k**). (b) UV−visible spectra of the water polluted with bisphenol A before and after gel shrinkage.

maintain the well-developed fiber structures even at elevated temperature so that the gel shrinks by expelling water instead of undergoing the conventional gel−sol transition. Thus, these small molecules acquire a unique thermoresponsive property as dynamic supramolecular polymers (Figure 4a).

This supramolecular hydrogel of the GalNAc-aa can release various water-soluble drugs and related molecules trapped in the gel matrix in a thermally controlled manner. Figure 5a, for instance, shows discontinuous release of DNA from the gel.[9] The accelerated leakage of DNA corresponds well to the phase transition temperature (*Tp*), implying that DNA is concurrently released upon the gel shrinkage. In contrast, bisphenol A, a hydrophobic water pollutant, was entrapped in the hydrophobic cavity of this gel **5k** and coprecipitated with the shrunken gel upon heating.[9] Two cycles of this coprecipitation carried out the perfect removal of bisphenol A (Figure 5b). Such a contrast catch-and-release behavior depending on the substances property can be reasonably ascribed to the amphiphilic characteristics of the present hydrogel. Thus, it is envisaged that the present supramolecular polymers bearing the dynamic thermal response offer access to a range of intelligent materials. The modular combination approach allows flexible adjustment of the molecular structure toward various objectives.

Supporting Information Available: Experimental details for synthesis of the GalNAc-aa, structural analysis (TEM, XRD, fluorescent spectroscopy), and DNA release and bisphenol A removal (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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