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(*S*)-(+)-Ibuprofen-based hydrogelators: an approach toward anti-inflammatory drug delivery

Sankarprasad Bhuniya, Young Jun Seo and Byeang Hyean Kim*

National Research Laboratory, Department of Chemistry, BK School of Molecular Science, Pohang University of Science and Technology, Pohang 790-784, Republic of Korea

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Abstract—We have synthesized (*S*)-(+)-ibuprofen-based hydrogelators that feature dipeptide linkages. In aqueous media, one of these hydrogelators formed robust gels that were stable for several months. Enzyme-mediated hydrolysis offers a route toward the sustained release of this anti-inflammatory agent.

The preparation of small organic molecules that are capable of gelling aqueous solvents (i.e., hydrogelators) is a rapidly expanding area of research,[1,2] especially because of these materials' possible practical applications in tissue engineering, as vehicles for controlled drug release,[3] and for the capture and removal of pollutants. A formidable challenge for controlled drug release is finding suitable biodegradable materials, which are usually polymeric in nature;[4] the use of small molecule gelators may overcome this problem because they can be derived from biocompatible components and because their gels are held together through noncovalent forces,[5] making them easier to degrade in vivo. In addition, the diversity of functionality, that is, available for the synthesis of such gelators opens up the possibility of incorporating drugs directly into the gelling component through covalent bonding, that is, without the need for physical entrapping. A further challenge for drug-based low-molecular-weight hydrogels[6] is the ability to facilitate drug delivery to targeted regions. In this letter, we report the synthesis of hydrogelators incorporating the anti-inflammatory drug (*S*)-(+)-ibuprofen, their gelation, and the drug's recovery through enzymatic cleavage, which may be beneficial for self-rendered anti-inflammatory activity. In addition, these hydrogelators may serve as carriers of other therapeutic agents because the arrest of inflammatory response is one of the most important prerequisites for biomaterials.

Scheme 1 illustrates our approach toward the synthesis of the (*S*)-(+)-ibuprofen-based gelators. Starting from commercially available (*S*)-(+) ibuprofen, we obtained the final products in overall yields of 60–70% after two successive coupling reactions with various amino acids.[7]

Of the six compounds that we prepared, only gelator **2a** had the ability to restrict the flow of water; its minimum gelation concentration (MGC) of 0.9% (w/w) suggests that one molecule of gelator **2a** traps 2000 water molecules (Table 1). In a mixed solvent system of water and ethanol, the MGC of gelator **2a** reached its minimum value (0.25%) at a H_2O-to-EtOH ratio of 80:20; that is, the MGC of this particular gelator depends on the polarity of the co-solvent system. In addition to **2a**, gelator **2f** also formed a gel in the 80:20 H_2O/ethanol co-solvent system (MGC = 0.5%). Gelator **2a** formed a translucent gel for each solvent system, whereas that of gelator **2f** was opaque; these gels were stable for several months. In case of gelators **2a** and **2f**, the balance between hydrophobic and hydrophilic forces is sufficient to form secondary structure (nano- to micrometer scale), that is, defined as the gel morphology; however, in other cases (**2b**–**e**) these forces are insufficient to stabilize secondary and tertiary structure of gelator in aqueous medium.[8]

Scanning electron micrograph (SEM) images (Fig. 1) of the cryo-dried hydrogels[9] of gelators **2a** and **2f** indicate that they existed as entangled irregular fibers having widths of 60–100 nm.

In both cases, these nanofibers were bundles of supramolecular polymer chains, suggesting that the intermolecular

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* Corresponding author. Tel.: +82 54 279 2115; fax: +82 54 279 3399; e-mail: bhkim@postech.ac.kr

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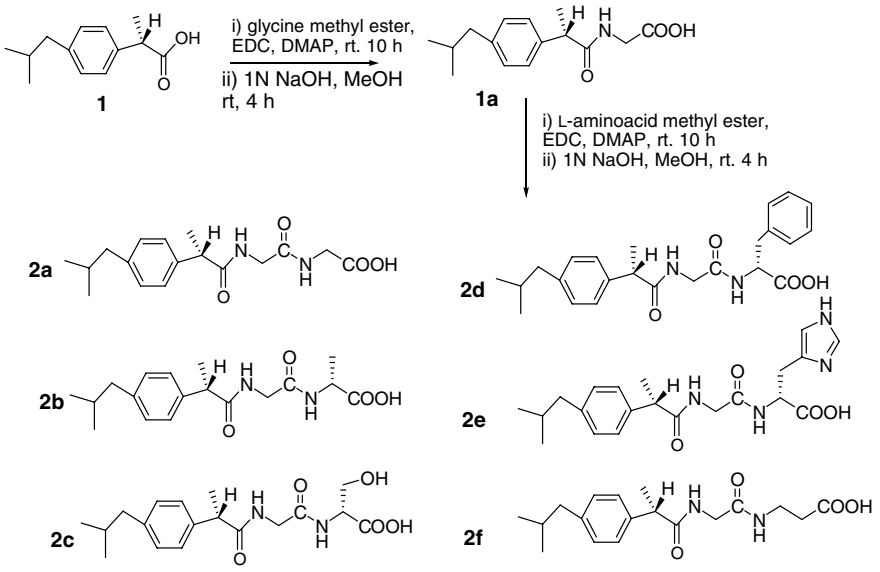

Scheme 1. Synthesis of potential hydrogelators.

interactions between the two types of gelators were similar.

To determine the roles played by the amide linkages and the carboxylic acid groups during the self-assembly, we recorded the FTIR spectra of gelator **2a** in both its solid amorphous and xerogel states.[7] The carbonyl stretching band of the carboxylic acid moiety shifted significantly (ca. 1733 cm^{-1}) in the gel state relative to its location in the solid amorphous state (ca. 1737 cm^{-1}). Similarly, the C=O stretching frequency of the amide group also decreased in the xerogel state when compared with that in its solid amorphous state. These spectral changes suggest that hydrogen bonding interaction of the carboxylic acid and the amide groups were one of the driving forces for gelation.

To obtain further information about the intermolecular hydrogen bonding interactions between amide groups, we measured the ^1H NMR spectra of **2a** in DMSO-d_6 containing various amounts of H_2O.[7] We found that upon increasing the H_2O content up to 20%, the signal for the amide proton initially shifted to lower field, but then shifted upfield at 30% H_2O. The changes in the chemical shifts of the amide protons, to lower fields in the aqueous solutions up to a 20% H_2O content, reveal that the hydrogen bonding with DMSO-d_6 $(CD_3)_2SO\cdots HN$ replaces that with $H_2O(H_2O\cdots HN)$.[10,11] Furthermore, the upfield shift of the amide NH signal at H_2O concentrations higher

Table 1. Gelation properties of hydrogelator **2a** in various solvent systems at 25 °C

H_2O:Ethanol	MGC[a] (w/w) %	Concentration (mmol)
100:00	0.90	28.00
95:05	0.60	18.75
90:10	0.40	12.50
85:15	0.30	9.35
80:20	0.25	7.80
75:25	0.40	12.50
70:30	0.50	15.60

[a] The MGC is the lowest gelator concentration at which gelation was observed to restrict the flow of the medium.

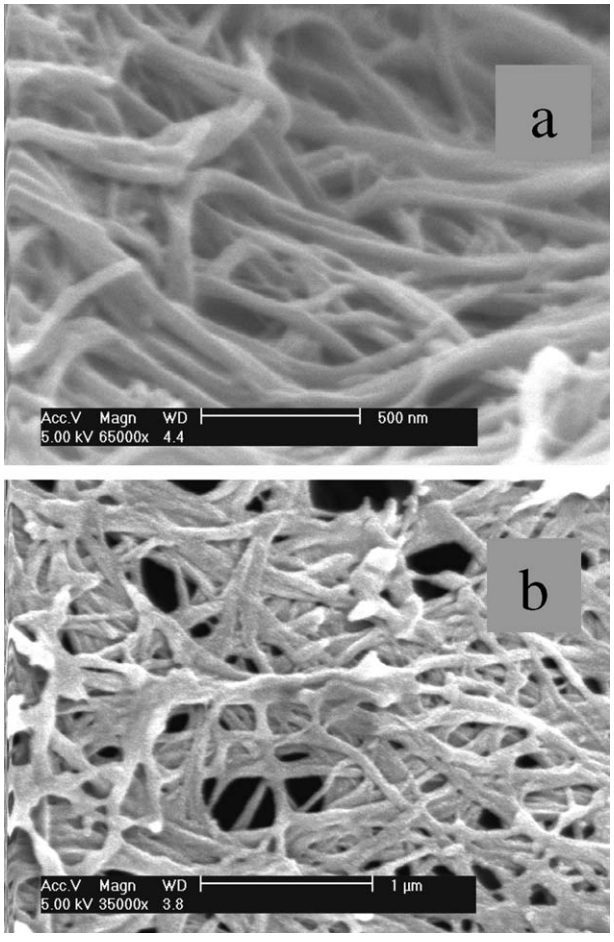

Figure 1. SEM images of the xerogels of gelators: (a) **2a** and (b) **2f**.

than 20% suggests that intermolecular hydrogen bonding occurred between the gelator molecules. In addition to these hydrogen bonds, we believe that hydrophobic interactions and van der Waals forces also play important roles during the gelation processes and in determining the architecture of the gel state.

To study the release of the drug, that is, (*S*)-(+)-ibuprofen, from gelator **2a**, we added a solution of carboxypeptidase Y (1 μmol, 0.02 mL) to a colloidal solution[12] of gelator **2a** (6 μmol, 2 mg). After incubation for 2 h at 37 °C, we acidified the solution to pH 2 and extracted it with EtOAc. We analyzed the organic extract using HPLC: the chromatogram we obtained was similar to that of ibuprofen itself (Fig. 2). This result encouraged us to attempt the release of the anti-inflammatory drug from its gel. Thus, we added a solution of carboxypeptidase Y (1 μmol; 0.02 mL) to the gel of gelator **2a**; after 24 h the gel became very weak—unstable with respect to inversion of the container (Fig. 3)—suggesting that the gel had been degraded by the enzyme.

In conclusion, we have synthesized potentially useful anti-inflammatory drug-based hydrogelators through simple peptide coupling reactions. The gelation ability of these gelators was dependent on the nature of the amino acid residues. Most importantly, we have demonstrated that it is possible to degrade such gels—and, hence, release the desired drug—through the action of an enzyme in vitro.

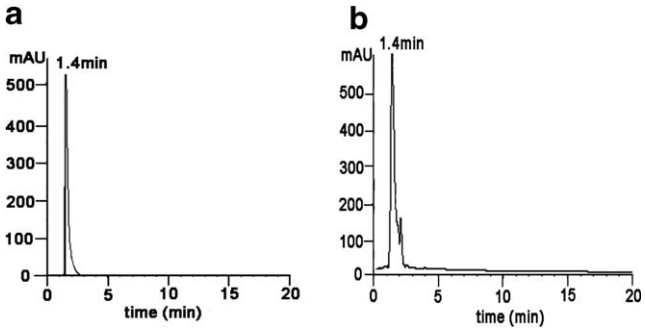

Figure 2. HPLC traces of (a) (*S*)-(+)-ibuprofen and (b) the organic extract of gelator **2a** after enzyme treatment. The HPLC mobile phase was held isocratically for 20 min with acetonitrile at a flow rate of 2.5 mL/min in silica column(Sigma–Aldrich, Spherlsorb Silica 5 μm, 4.6 mm × 250 mm).

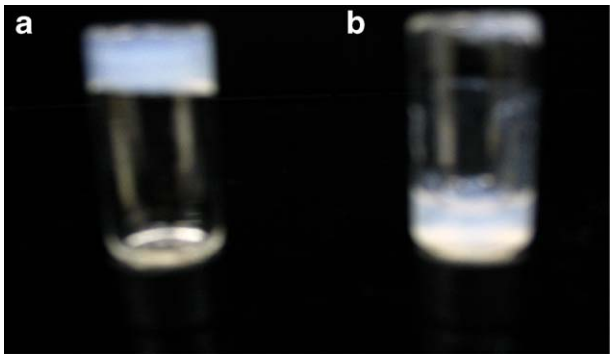

Figure 3. Photographic images of the gels of gelator **2a**: (a) before and (b) after addition of the enzyme.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.002.

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12. Gelator **2a** (0.2 mg) was placed in 1 mL buffer solution (pH 7; 0.5 mL) and warmed for 5 min at 60 °C to form a colloidal suspension. The enzyme solution (buffer, pH 7; 1 μmol, 0.2 mL) was then added and the solution was incubated for 2 h at 37 °C. Then the solution was acidified to pH 2 at rt, then extracted with EtOAc, and subjected to HPLC analysis.