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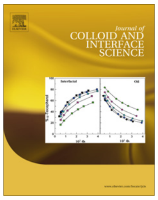

Amphiphilic sulfamide as a low-molecular-mass hydrogelator: A novel mode of 3-D networks formed by hydrogen-bond-directed 2-D sheet assemblies

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ABSTRACT

Asymmetrically substituted amphiphilic sulfamide, *N*-tetradecyl-*N*′-(6-dimethylaminohexyl)-sulfamide (**3c**) having a dimethylamino group at one end of the side chain, showed a strong ability to form two-dimensional (2-D) sheet-like assemblies by the 2-D hydrogen-bond networks between sulfamide moieties. Upon protonation of the amino group with acid, the cationic ammonium form of **3c** induced effective hydrogelation (minimum gelation concentration: 0.5 wt%) to yield a translucent, self-standing hydrogel. Infrared (IR) spectroscopy, X-ray diffraction (XRD), atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) studies confirmed formation of the fibrous assemblies of the hydrogen-bond-directed 2-D nanosheets in the hydrogel. A novel mode of three-dimensional (3-D) networks was formed by branching and recombination of hydrogen-bond networks and knit-like linkages between the assemblies. The storage and loss moduli of the hydrogel (2 wt%) were measured to be in the range of 10^2 and 10^3 Pa, showing relatively high mechanical stability.

1. Introduction

In recent years, supramolecular gels formed by low-molecular-mass gelators (LMGs) [1–3] have been attracting increasing attention due to their potential applications such as drug delivery systems [4,5], scaffolds for tissue engineering [6,7], and other stimuli-responsible materials [8,9]. Because of the dynamic nature of intermolecular interactions, supramolecular gels are expected to show high responsibility to external stimuli. In a typical supramolecular gel, LMGs are connected by noncovalent bonds to form one-dimensional nanofibers and three-dimensional (3-D) networks of the fibrous assemblies by cross-linking and physical entanglement induce gelation of the solvents [10,11]. Since noncovalent interactions are much less robust and weak compared to covalent bonds, fabrication of macroscale assemblies from the nanoscopic-scale LMGs in a predictable way is difficult to achieve. It is well recognized that hydrogels play important roles in food, cosmetics, pharmaceuticals, and many other fields and have been intensively studied [12–17]. Although increasing numbers of reports have appeared recently [18–23], those on supramolecular gelators that are effective for inducing gelation in water are still limited [24–28]. This may be due to the fact that a hydrogen bond, which has been used widely as a key interaction for fabrication of the 3-D network of LMGs [29,30], does not effectively operate in water. The hydrogen bond is the effective interaction among the noncovalent interactions because of its relatively strong and directional nature. Therefore, it is a challenging target to study the rational design concept of a supramolecular hydrogelator based on the effective hydrogen-bonding interaction.

We previously reported that the two-dimensional (2-D) hydrogen-bond network of sulfamide derivatives forms hydrogels [31] and vesicles [32] in water. A design concept for fabrication of the hydrogen-bond-directed nanosheet assemblies has been developed by using guanosine derivatives [33–35] and the concept was successfully applied to sulfamide derivatives. Proper design of the side chains to protect the hydrogen-bonding moiety and robust multiple hydrogen-bond interactions of the sulfamide units allowed formation of the 2-D hydrogen-bond network even in water. *N*,*N*′-Disubstituted sulfamide derivatives are shown to serve as LMGs for aqueous, organic, and aqueous/organic biphasic systems by the formation of hydrogen-bond-directed 2-D sheet assemblies [31]. However, the organo- and hydrogels of the sulfamide gelators were not sufficiently tough against external forces because the amount of cross-linking between nanosheet assemblies was insufficient.

Herein, we report that an asymmetrically substituted amphiphilic sulfamide derivative having a dimethylammonium group at one end of the side chain is a new class of effective supramolecular hydrogelator. Hydrogelation is induced by formation of the hydrogen-bond-directed and flattened fibrous 2-D sheet assemblies and

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their novel mode of 3-D networks. High mechanical stability is discussed in view of the gel structure.

2. Experimental section

2.1. Materials

The reagents and solvents were purchased from Sigma–Aldrich Co., Tokyo Chemical Industry Co., Kanto Chemical Co., and Wako Pure Chemical Industries. When necessary, the chemicals were dehydrated and distilled by routine procedures. Synthesis of the sulfamide derivatives was carried out by the same procedure described previously [31].

2.2. Sulfamide derivatives 3

3a: White solid. Mp 98.1–99.0 °C. ^{1}HNMR (400 MHz, $CDCl_3$) 0.86–0.91 (3H, t, $-CH_2-CH_3$), 1.25–1.54 (20H, m, $-CH_2-$), 2.21 (6H, s, $-N(CH_3)_2$), 2.22–2.27 (2H, t, $-CH_2-N<$), 3.00–3.07 (4H, q, $-NH-CH_2-$), 4.04 (1H, t, $-NH-C_8H_{17}$), 4.23 (1H, t, $-NH-(CH_2)_6-N(CH_3)_2$). HR-MS: $m/z = 336.2678$ (calcd. for $(M+H)^+$: 336.2684).

3b: White solid. Mp 84.6–85.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 0.86–0.90 (3H, t, $-CH_2-CH_3$), 1.26–1.76 (26H, m, $-CH_2-$), 2.24 (6H, s, $-N(CH_3)_2$), 2.42–2.46 (2H, t, $-CH_2-N<$), 3.02–3.16 (4H, q, $-NH-CH_2-$), 4.14 (2H, t, $-NH-$). HR-MS: $m/z = 378.3145$ (calcd. for $(M+H)^+$: 378.3154).

3c: White solid. Mp 92.5–92.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 0.86–0.90 (3H, t, $-CH_2-CH_3$), 1.26–1.53 (32H, m, $-CH_2-$), 2.21 (6H, s, $-N(CH_3)_2$), 2.23–2.27 (2H, t, $-CH_2-N<$), 3.00–3.07 (4H, q, $-NH-CH_2-$), 4.01–4.04 (1H, t, $-NH-C_{14}H_{29}$), 4.20–4.23 (1H, t, $-NH-(CH_2)_6-N(CH_3)_2$). HR-MS: $m/z = 420.3619$ (calcd. for $(M+H)^+$: 420.3623).

2.3. Titration

To estimate the degree of ionization, titration of sulfamide derivatives having amino group **3c** was tested. Since **3c** was not soluble in water, THF was used as a supporting solvent and **3c** was dissolved in water–THF solution (1:3 vol) at a concentration of 0.1 g/mL. To this solution, 10 mM HCl aq. was added dropwise and the pH was monitored by a pH meter throughout the experiment.

2.4. Gel preparation

In a 5 mL glass-made vial, desired amounts of the sulfamide derivatives were dispersed in water, followed by adding appropriate quantities of 1 M HCl aq., if necessary. The total volume was adjusted ca. 1 mL. The mixture was heated at 100 °C, above the melting point of the sulfamide derivatives, for 10 min. The resultant clear solution was then cooled down to room temperature without intentional flow of air.

2.5. Infrared spectroscopy

IR spectra of cast films on the CaF_2 substrates were taken by using SHIMADZU FTIR-8700.

2.6. X-ray diffraction

A Rigaku RINT-2100 diffractometer (Cu Kα) was used for the XRD measurement of the cast films on the glass substrate and powder samples of xerogels.

2.7. Transmission electron microscopy

JEOL JEM-1011 was used for TEM observation by the freeze-fracture-replica method. Preparation of the sample was done as follows. The hydrogel of **3c**/HCl (2 wt%) mixed with same weight of 60 wt% glycerin aq. was frozen by N_2 slash, cut, and shadowed by Pt and carbon.

2.8. Scanning electron microscopy

For SEM observation, HITACHI TM-1000 was used. The hydrogels of **2** (5 wt%) and **3c** (2 wt%) were freeze-dried and the SEM images were taken without any deposition.

2.9. Atomic force microscopy

For observation of the hydrogel of **3c** (2 wt%), Shimadzu SPM9500J3 was used. The sample was prepared by three methods. (1) The hydrogel was directly transferred onto a silicon substrate. (2) The hydrogel was dried under ambient conditions overnight. (3) The hydrogel was diluted 100 times by water, then casted, and dried on a silicon substrate. Each sample was scanned by using dynamic mode.

2.10. Rheology measurements

Rheological properties were measured on an Anton Paar Physica MCR301 rheometer with a 50 mm cone (1° angle) on the top. The strain γ was set at 10% for lower sulfamide concentration (0.5 wt%) and 1% for higher ones (1 and 2 wt%).

3. Results and discussion

3.1. Molecular design

The symmetrically substituted derivative **1b** induced gelation of varieties of organic solvents, including ethanol and dodecane, by formation of 2-D nanosheets [31], but **1b** was insoluble in water because of highly hydrophobic tetradecyl side chains. However, by introducing a hydrophilic glyceryl unit at one end of the alkyl chain, asymmetrically substituted sulfamide **2** became soluble in hot water and formed a hydrogel upon cooling [31]. To extend the strategy further, we introduced more hydrophilic ammonium groups as end groups to cover the surface of the 2-D nanosheets. The dimethylamino group, the size of which is smaller than the unit area of sulfamide (0.25 nm^2) [36], was chosen as the end group in order to avoid destruction of the hydrogen-bond network due to steric crowding. The dimethylamino group can be converted to the cationic ammonium form by neutralization with acid. Because the appropriate balance of hydrophobicity and hydrophilicity of the side-chain structures is thought to be the essential factor in effective hydrogelation, we prepared **3a**–**c** having different alkyl chain length as the hydrophobic moiety. The derivatives **3a**–**c** were synthesized stepwise by using 4-nitrophenol as a protecting group [37] and were obtained as white solids.

3.2. 2-D sheet assemblies of neutral sulfamide derivatives

A model compound, *N,N′*-dioctyl sulfamide **1a**, forms a robust grid-type 2-D hydrogen-bond network in a crystal, with two octyl substituents extending toward opposite directions from the sulfamide network plane (Fig. 1b and c) [38,39]. Cast films of **3a**–**c** on a CaF_2 or glass plate from their chloroform solutions were homogeneous and translucent, but only a powdery coating was obtained in the case of compound **1b**. The infrared (IR) spectra of the