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Formation of supramolecular hydrogels with controlled microstructures and stability via molecular assembling in a two-component system

Jiwei Wu, Liming Tang *, Kai Chen, Liang Yan, Fei Li, Yujiang Wang

Laboratory of Advanced Materials, Department of Chemical Engineering, Tsinghua University, Beijing 100084, People's Republic of China

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Abstract

Two isomeric building units, 4-oxo-4-(2-pyridinylamino) butanoic acid (defined as G1) and 4-oxo-4-(3-pyridinylamino) butanoic acid (defined as G2) formed fiber- and tree-like crystals in aqueous solutions, respectively. The crystal formation process of G1 was suggested based on the layered cross section of an individual crystal and the single crystal structure. Through cooling the aqueous solutions of their mixtures under G1/G2 molar ratios ranged from 7/1 to 1/3, a series of supramolecular hydrogels were formed based on hydrogen bonds as the main driving force. As decreasing G1/G2 ratios, the first observed aggregates in solution changed from fiber to particle form, while the gelating time became longer and longer. At the collapsing temperature, the gels formed at G1/G2 ratio $\geqslant 3/1$ kept the original gel shape but released water, while at G1/G2 ratio $\leqslant 2/1$ they broke into pieces without releasing water. The "dropping ball" experiment indicated that the highest gel-to-sol dissociation temperature (T_{gel}) is obtained at G1/G2 ratio of 2/1. As measured by UV–vis spectroscopy, the two building units distributed uniformly within the gel formed at G1/G2 ratio of 1/1, indicating they assembled together in forming hydrogel. The scanning electron microscope (SEM) and infrared spectrometer (FT-IR) analysis of the dried samples indicated that the backbone shape changed from fiber to sheet and the content of free carboxyl groups increased with decreasing G1/G2 ratios, therefore resulting in hydrogels with different stability. The simple gelator structures and the possibility in controlling gel structure and stability make the hydrogels suitable for various uses.

Keywords: Supramolecular hydrogel; Hydrogen bonding; Molecular assembling; Gel structure and stability

1. Introduction

Small molecular organic hydrogelators [1,2] that are capable of gelating aqueous solvents have gained great attention recently due to their scientific values and many potential applications in biomedical field, including tissue engineering, controlled drug release, medical implants, and so on [3,4]. In general, these molecules demonstrate amphiphilic characters in water with hydrophobic groups promoting aggregation and hydrophilic groups providing solubility and attraction force to water molecules [5]. According to Hamilton's recent review [1], many different kinds of amphiphilic molecules can be used as effective hydrogelators, including conventional amphiphiles [6] with one polar head group and one or two hydrophobic tails, bolaamphiphiles [7] with two polar heads connected by a hydrophobic linker, gemini surfactants [8,9] with flexible tail–ion–linker–ion–flexible tail structure, sugar-based systems [10], and so on. In addition to one-component systems, hydrogels can be formed in two-component systems as well [11]. For example, Zhang et al. [12] described supramolecular hydrogels with improved mechanical strength based on vancomycin and D-Ala–D-Ala derivative. However, almost all these hydrogelators possess rather complex structures and thus make it difficult to study the gel formation mechanism. In 2003, Hamilton described a series of mono-urea derivatives and found that the smallest hydrogelator has a molecular weight of only 232 Da [13], which might be the simplest hydrogelator even at present. Based on the fundamental investigations, it is generally accepted that the gelators form three-dimensional networks through intermolecular interaction and trap the solvent to form the gel via the non-covalent interaction [14]. However it is still not fully understood how the gelator molecules assemble step-by-step into aggregates and even more complicated structures,

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* Corresponding author. Fax: +86 010 62770304.
E-mail address: tanglm@tsinghua.edu.cn (L. Tang).

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and how the solvent molecules interact with the aggregating backbones within the gel.

To make the hydrogelators assembling into aggregate form in water, the aggregation driving force must be designed into the molecules, which is mostly depended on hydrophobic force [15], and sometimes on salt bridges and transition metal coordination [16]. It is well known that hydrogen bonds play an important role in organisms and become a common driving force for intermolecular aggregation in organogel systems [17]. Due to the destructing by water molecules, hydrogen bonds have seldom been designed into hydrogel systems [18,19]. It has been well known that many simple organic molecules form stable crystals in water based on hydrogen bonds as the driving force. However, due to the lack of sufficient hydrophilicity, the crystals precipitate out of water rather than assemble into supramolecular hydrogels. To make the crystal suitable as water gelators, the molecular amphiphilic balance must be controlled to such an extent that the aggregates display sufficient attraction to water molecules. On the other hand, the pair of carboxyl and pyridyl groups has been frequently designed into supramolecular systems because of their capability to form stable hydrogen bond [20]. Under water environment, through forming hydrogen bond between carboxyl group and pyridyl group to decreasing the hydrophilicity, the amphiphilic balance of the resulting structure is possible to reach such an extent that the molecular aggregation becomes possible. Therefore, the molecules with both carboxyl and pyridyl groups should be adequate candidates for hydrogelators. With this in mind, in our previous article we designed a kind of supramolecular building unit bearing both of the groups from 1,2,4,5-benzenetetracarboxylic acid and 4-hydroxypyridine. Under suitable conditions, supramolecular hydrogels were formed from the building unit through hydrogen bonds of the donor and acceptor groups [21].

In this paper, we designed two isomeric building units, 4-oxo-4-(2-pyridinylamino) butanoic acid (defined as G1) and 4-oxo-4-(3-pyridinylamino) butanoic acid (defined as G2), both of which caring carboxyl and pyridyl groups and forming different crystals in water. To our surprise, when cooling the hot aqueous solutions of their mixtures in air at 25 °C, hydrogels rather than crystals were obtained. The present two-component system is quite different from the traditional two-component gelation systems where two distinct, complementary components are used [11]. To our knowledge, hydrogelators with such simple structures have not yet been reported. Besides that, it is interesting to find that the gel structure and stability can be controlled simply via the ratio of the two components. The simple gelator structures and the easy control over gel structure and stability should make the hydrogels suitable for various purposes.

2. Experimental

2.1. Materials

3-Aminopyridine (regent grade, 99.0%) was purchased from Beijing Chemical Regent Company. 2-Aminopyridine (chemically pure) was purchased from Beijing Medicine Company. Succinic anhydride (chemically pure) was purchased from Shanghai Lingfeng Chemical Regent Co. Ltd. All the other reagents were all of analytical grade and were used as received.

2.2. Synthesis of G1 and G2

G1 was synthesized by the following procedure: 2.1 g (0.021 mol) succinic anhydride, 1.88 g (0.02 mol) 2-aminopyridine and 35 mL DMSO were dissolved in a flask equipped with a magnetic stirrer and a reflex condenser. After reacted at a constant temperature of 50 °C for 4 h, the solution was slowly added into 200 mL chloroform. After one night storage, the white precipitate was collected and dried in an oven under vacuum to a constant weight. The product G1 was obtained as white powder in 55.3% yield. The elementary analysis, found: C 55.33, H 5.233, N 14.233. Calculated for $C_9H_{10}N_2O_3$: C 55.67, H 5.16, N 14.43. ^{1}H NMR (δ/ppm): 12.12 (H, COOH), 10.49 (H, NH), 8.29 (H, 6-pyridyl H), 8.04–8.06 (H, 3-pyridyl H), 7.74–7.77 (H, 4-pyridyl H), 7.06–7.08 (H, 5-pyridyl H), 2.63–2.64 (2H, CH_2), 2.51 (4H, CH_2) (overlapped by solvent). FT-IR (KBr, ν, cm^{-1}): 3315 and 3259 (–NH–, hydrogen bond), 2486 (hydrogen bond of pyridyl N≡HO), 1695 (for both amide C=O and hydrogen bonded carboxylic C=O).

By the same method as G1, G2 was prepared from succinic anhydride and 3-aminopyridine as white powder in 55.2% yield. The elementary analysis, found: C 54.93, H 5.24, N 14.10. Calculated for $C_9H_{10}N_2O_3$: C 55.67, H 5.16, N 14.43. ^{1}H NMR (δ/ppm): 12.16 (H, COOH), 10.18 (H, NH), 8.72 (H, 2-pyridyl H), 8.23–8.24 (H, 6-pyridyl H), 8.01–8.03 (H, 4-pyridyl H), 7.31–7.34 (H, 5-pyridyl H), 2.58–2.60 (2H, CH_2), 2.53–2.54 (2H, CH_2). IR (KBr, ν, cm^{-1}): 3311 and 3270 (–NH–, hydrogen bond), 2432 (hydrogen bond of pyridyl N≡HO), 1726 (free carboxylic C=O), 1687 (for both amide C=O and hydrogen bonded carboxylic C=O).

2.3. Formation of G1 and G2 crystals

The formation procedure for G1 crystals is described as follows: 0.08 g (0.412 mmol) G1 was added into 1.92 g de-ionized water in a glass tube to form a suspension. After heated in an oil bath preheated at 95 °C, the suspension gradually turned into a transparent solution. The tube was taken out and stored at 25 °C. After only 8 min, white fiber-like crystals were formed in the tube. By the same method, tree-like G2 crystals with many branches were obtained after 24 h storage at 25 °C.

2.4. Formation single crystal of G1

0.3 g G1 was dissolved in 300 mL de-ionized water in a glass bottle. After storage at 25 °C for one month, the formed single crystal was taken out and dried in an oven under vacuum to a constant weight. X-ray diffraction measurement of the single crystal was performed on Bruker P4 Diffractometer equipped with graphite monochromatized Mo$K\alpha$ radiation. All hydrogen atoms were generated geometrically with C–H, N–H, and O–H bond distances of 0.82–0.97 Å according to criteria described in the SHELXTL manual (Bruker, 1997) [22]. Data collection was controlled by XSCANS program (Bruker,