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A New Dual-Responsive Organogel Based on Uracil-Appended Glycyrrhetinic Acid

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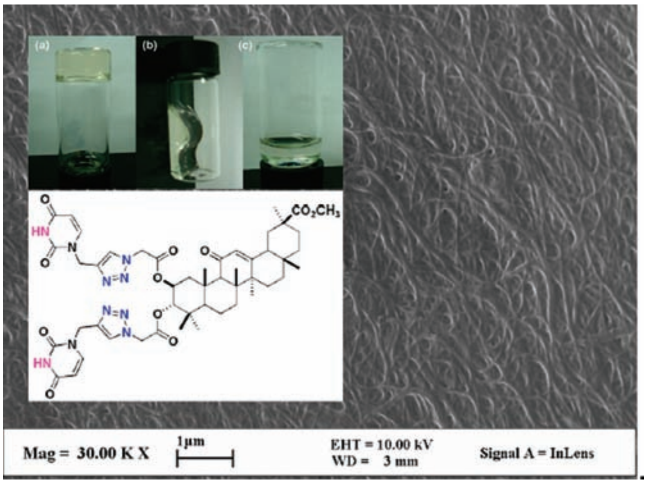
ABSTRACT



A novel functional tweezer based on uracil-appended glycyrrhetinic acid with excellent gelation ability was synthesized, and the gel could transform to sol by F^- and Hg^{2+}.

Organogels, which are various three-dimensional aggregates with micrometer-scale lengths and nanometer-scale diameters immobilizing the flow of liquids, have been known for potential applications on materials, drug delivery, agents, and sensors as well as water purification.[1] The driving forces responsible for gel formations are specific or noncovalent interactions such as the dipole–dipole interaction, van der Waals forces, and hydrogen bonding. In particular, complementary hydrogen bonding patterns play a very important role in forming both mono- and multicomponent architectures,[2] and their application in the fabrication of organogels has been attempted.[3] Recently

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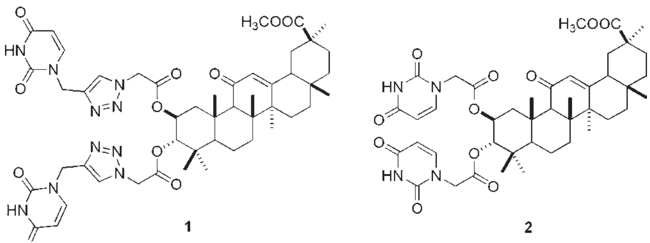

Figure 1. Glycyrrhetinic acid-based tweezer **1** and compound **2** as a control.

the different reversible sol–gel transitions in gelators responsive to light,[4] redox,[5] counterions, or molecules[6] and pH[7] were reported. The reversibility as a crucial feature of supramolecular materials enables these smart gels superior to conventional ones and brings accessibility for designing new functional materials.

Glycyrrhetinic acid, a facile natural pentacyclic triterpenoid, possesses special characteristics such as a chiral rigid skeleton, relative low toxicity, and biocompatibility. It is mainly used for anti-inflammation, antivirus, and antitumor treatments.[8] Recently, there have been more reports about using the triterpenoids as building blocks in supramolecular recognition[9] and assembly[10] since their special characteristics could offer diversity spacer and unique spatial structure arrangement. Meanwhile, nucleobases involved in the self-assembly of DNA and RNA are being investigated for supramolecular behavior[11] toward a better understanding of how molecules interact with each other. In particular, uracil was reported as the building block in constructing functional molecules not only in biology but also in supramolecular chemistry and nanotechnology.[12] In addition, 1,2,3-triazoles are being explored as binding sites[13] in addition to being attractive connecting units by click reaction.[14]

As a continuation of our previous work on the functional molecules based on triterpenoids,[9b,15] we report the synthesis of a tweezer **1** (Figure 1) based on uracil-appended glycyrrhetinic acid linked by 1,2,3-triazole and its gelation properties with stimuli-responsive behavior of ions attributed to the 1,2,3-triazole and uracil.[16]

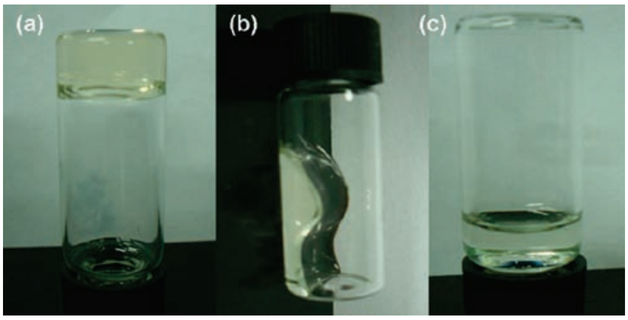

Figure 2. State changes during the melting process of the gel **1** (0.7 g/100 cm^3) in 1,2-dichloroethane: (a) gel obtained at 20 °C; (b) gel–sol phase at 42 °C; (c) solution above 42 °C (the T_{gel} of **1** in 1,2-dichloroethane).

Compound **1** was synthesized from the 2,3-dihydroxyglycyrrhetinic acid methyl ester[9b] (Scheme 1 in the Supporting Information). The gelation behaviors of **1** were determined in various solvents by a "stable to inversion of the test tube" method,[17] and transparent, stiff, and thermoreversible gels were observed in a series of halohyrocarbon solvent (Figure 2), which were stable and remained for more than 3 months at room temperature without any changes (Table 1; Figure S1, Supporting Information). The results showed that 1,2-dichloroethane is one of the best solvents for the gelation process by

Table 1. Physical Data for Gels of **1** in Various Organic Solvents

entry	solvent	state[a]	MGC (g/100 cm^3)[b]
1	CH_2Cl_2	G	1.8
2	$CHCl_3$	G	3.8
3	1,2-dichloroethane	G	0.33
4	1,3-dibromopropane	G	0.45
5	CCl_4	I	
6	methanol	P	
7	isopropyl alcohol	I	
8	acetonitrile	P	
9	acetone	S	
10	THF	S	
11	DMF	S	
12	toluene	I	
13	chlorobenzene	S	
14	1,2-dichlorobenzene	S	
15	nitrobenzene	S	

[a] G = stable gel, S = soluble, I = insoluble, P = precipitate. [b] MGC is the minimum gelator concentration at which gelation was observed to restrict the flow of the medium at 25 °C.

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comparing MGC at room temperature (Minimum Gelator Concentration) in different measured solvents.

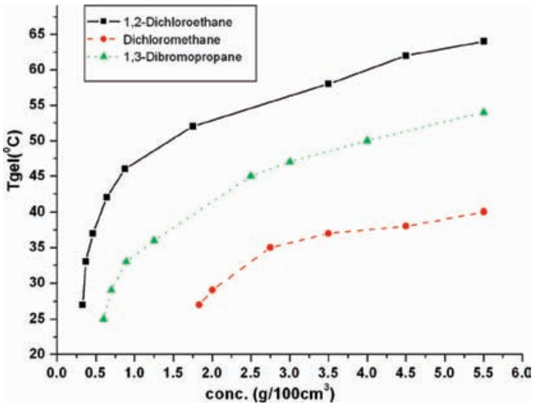

Figure 3. Plot of T_{gel} vs concn of **1** in 1,2-dichloroethane, dichloromethane, and 1,3-dibromopropane.

In order to determine the thermal stability of the gels, T_{gel} defined as the required temperature for the organogel to collapse was measured by the dropping ball method[18] and plotted against the gelator concentration (Figure 3). Obviously, the T_{gel} increased with the increase of the concentrations of gelator **1**. On the basis of these data, the thermodynamic parameters ($\Delta H°$, $\Delta S°$, and $\Delta G°$)[19] at 298 K of gels during melting in various solvents were calculated (Table 2). It showed that values of $\Delta G°$ were in accordance with the T_{gel} of **1** in different solvents, and proved the gel of **1** in 1,2-dichloroethane had an excellent gelation ability.

Table 2. Thermodynamic Parameters ($\Delta H°$, $\Delta S°$, and $\Delta G°$) of Gels during Gel Melting in Various Solvents at 298 K

solvent	$\Delta H°$ (kJ/mol)	$\Delta S°$ (J/mol/K)	$\Delta G°$ (kJ/mol)
1,2-dichloroethane	83.6 ± 6.7	205.1 ± 21.2	22.7
1,3-dibromopropane	54.5 ± 4.4	121.2 ± 14.5	18.5
dichloromethane	64.4 ± 6.6	162.3 ± 21.5	16.2

To gain visual insight into the aggregation mode and microscopic morphology of this organogelator, scanning electron microscopy (SEM) was used to investigate the assembly structure. The SEM images of the gel in chloroform revealed a nanoscale fibrous structure with regular fiber diameters of ca. 30–60 nm, and this assembly created a closely packed 3D network structure by entanglement of such nanofibers which trapped the solvent molecules into its interstices (Figure 4). In the case of xerogel from the same solvent, a lamellar morphology was also observed (Figure S2, Supporting Information), and it was also supported by XRD analysis (Figure S3, Supporting Information). The xerogel of **1** exhibited broad X-ray diffraction patterns which were characteristic of the long-range ordering of the molecules.

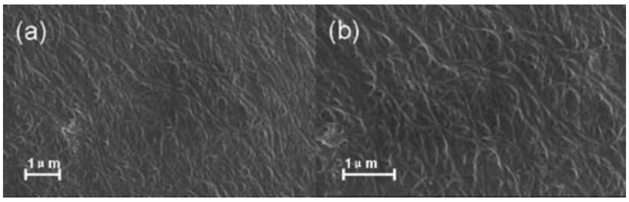

Figure 4. Scanning electron micrographs of gel from **1** (5.0 g/100 cm^3) in chloroform.

The variable-temperature ^{1}H NMR of gel **1** in $CDCl_3$ were performed to determine the driving forces. The results showed that the NH resonance signals were gradually shifted upfield and became sharper and shaper as the temperature rose (Figure S4, Supporting Information). It revealed that hydrogen bonding was involved in the gel formation. In addition, the results from concentration-dependent ^{1}H NMR experiments also confirmed that the hydrogen bonding formed by NH protons took participate in the gel formation (Figure 5).

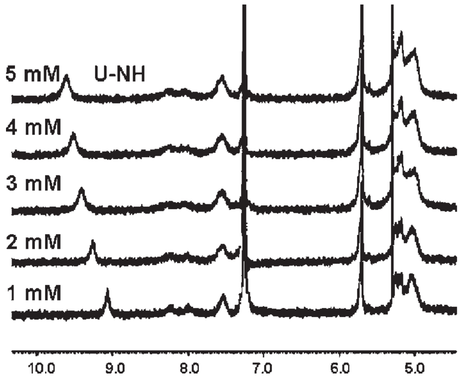

Figure 5. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$) of **1** at different concentrations at 25 °C.

Compound **2** without 1,2,3-triazole was also synthesized as the control (Scheme 2 in the Supporting Information), and it displayed no gelation abilities, which suggested that $\pi-\pi$ interaction between 1,2,3-triazoles also played a synergic effect in formation of the gel besides intermolecular hydrogen bonding. It was further verified by comparing the UV–vis spectra of gel **1** with its solution in

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1,2-dichloroethane, which exhibited an obvious red-shift band (Figure S5, Supporting Information). The same red-shift band also appeared with a lower intensity gel sample, so it eliminated interference caused by different concentrations between the gel and the solution.

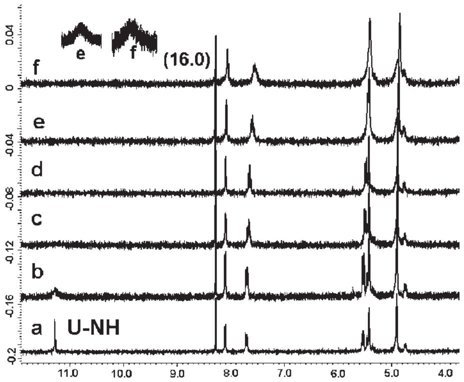

Figure 6. Partial ^{1}H NMR spectra of **1** (5 mM) in DMSO-d_6 upon the addition of F^-: (a) free; (b) 0.5 equiv of F^-; (c) 1 equiv of F^-; (d) 2 equiv of F^-; (e) 3 equiv of F^-; (f) 4 equiv of F^-.

It was known that anions can form hydrogen bonding with reactive hydrogen, and some anion-tuning organogels were reported.[20] Thus, the effect of anions on the gelation process was investigated by repeating the gelation experiments of **1** in the presence of different anions (F^-, Cl^-, Br^-, I^-, as ^{n}Bu$_4$N$^+$ salt). The 1,2-dichloroethane gel of **1** became unstable and eventually turned into a homogeneous solution on addition of 1 equiv of F^-, while the gel of **1** was still stable after addition of other halide anions (Cl^-, Br^-, I^-) (Figure S6, Supporting Information). The ^{1}H NMR titration experiments showed that the NH resonance signals became weaker and finally disappeared completely as the concentrations of F^- in the gel increased (Figure 6), which might be due to the formation of hydrogen bonding between F^- and reactive hydrogen.[21] The intermolecular hydrogen bonding was destroyed, and it resulted in the change of gel to sol. Meanwhile, a new weak broad signal appeared at δ 16.0 ppm implying the formation of HF_2^- (Figure 6A.f),[22] while no shift was observed with regard to other halide anions because of the weaker basicities compared to F^- (Figures S7–S9, Supporting Information).

The role of 1,2,3-triazole was realized to provide a coordination site in the formation of stable metal complexes.[13] The gel stability of **1** was also tested by the influence of Hg^{2+}, Mg^{2+}, Cu^{2+}, Cd^{2+}, and Zn^{2+} as perchlorate salts. With progressive addition of more than 2 equiv of these cations, only the gel phase treated with Hg^{2+} was transformed to the homogeneous solution, and other gels phase were stable with Mg^{2+}, Cu^{2+}, Cd^{2+}, and Zn^{2+} (Figure S10, Supporting Information). The results clearly demonstrated that the gel phase had the selective responsive nature to metal cations. UV–vis spectra were obtained to evaluate the recognition ability of **1** toward metal cations (Figure 7). Consequently, it was found that compound **1** showed significant intense variation of their absorption spectra upon the addition of Hg^{2+}. However, the UV–vis spectra showed negligible changes after the addition of other cations (Mg^{2+}, Cu^{2+}, Cd^{2+}, and Zn^{2+}). The Job's plot indicated the 1:1 complex formation, and the binding constant was calculated to be 3.9×10^3 M^{-1} using the Hildebrand–Benesi equation (Figures S11 and S12, Supporting Information).[23] The mechanism should be similar to that mentioned in our previous report.[9b] The binding behavior of 1,2,3-triazole with Hg^{2+} destroyed $\pi-\pi$ interaction between 1,2,3-triazoles, which resulted in the collapse of the gel.

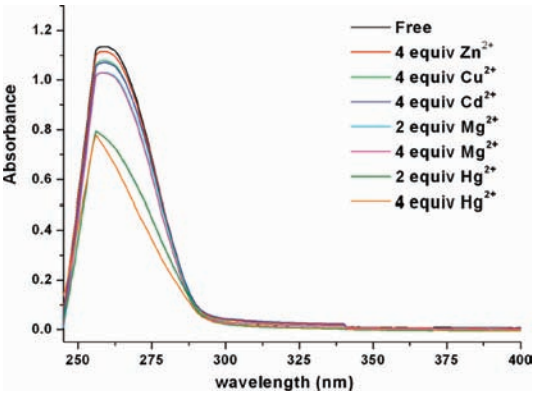

Figure 7. UV–vis absorption spectra of **1** (6×10^{-5} M) in the presence of various cations in CH_3OH at room temperature.

In conclusion, a novel uracil-appended glycyrrhetinic acid conjugate was synthesized, and its gelation characteristics were studied. The gel-to-sol phase transition process could be selectively controlled by interaction with both cations and anions such as F^- and Hg^{2+}. Because of the novel gelation property of the glycyrrhetinic acid conjugate, a natural facile triterpenoid with low-toxicity, biocompatibility, and bioactivity, it may be successfully applied for construction of a new class of stimuli-responsive soft materials and lead to potential applications in biomedical engineering and the drug industry.

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Supporting Information Available. Synthesis and structure data of compounds **1** and **2**, thermodynamic parameters, and some results of ion effects on gel. This material is available free of charge via the Internet at http://pubs.acs.org.

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