Novel low-molecular-weight hydrogelators based on 2′-deoxyuridine

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We have synthesized low-molecular-weight, triazole ring-appended 2′-deoxyuridine hydrogelators that gelate pure water at a concentration as low as 0.2 wt% and these compounds display different aggregation and network structures as evidenced by their SEM images, FTIR spectra and minimum gel concentrations.

Hydrogelators are very useful materials for biomedical applications, for example, in tissue engineering, drug delivery systems and medical implants.[1] Although several classes of hydrogelators have been reported recently, only a few of them[2–5] form gels in pure water, which is an important and necessary requirement for biomedical applications. Organo/hydrogelators based on DNA derivatives are few in number.[2,6,7] Last year, the first hydrogelator based on thymidine was reported for hydrogelation using nucleotide-appended bolaamphiphiles.[2] In this paper, we report a new class of hydrogelators, which are based on the nucleoside 2′-deoxyuridine, that have good hydrogelation abilities (0.2–3 wt%, pure water) and comparatively low molecular weights. We have synthesized these efficient hydrogelators by simple modifications of the base moiety of 2′-deoxyuridine.†

Previously, we have reported the preparation of nucleoside-based organogelators.[6] To form these organogels, we introduced a long hydrocarbon chain and bulky protecting groups onto thymidine. In the case of a hydrogelator, however, it is important to control the balance between hydrophilicity and hydrophobicity. 2′-Deoxyuridine itself is very hydrophilic because it contains many functional groups capable of hydrogen bonding. To control the hydrophilic/hydrophobic balance, hydrophobic moieties need to be introduced, but it is not just a simple matter of increasing the hydrophobicity: we must also increase the aggregation ability. After some investigations by trial and error, we introduced several benzyltriazole ring derivatives at the C5 position of 2′-deoxyuridine. Heterocyclic moieties, especially those containing nitrogen atoms, are often introduced in the synthesis of polymeric and monomeric hydrogelators.[4,8] The triazole units increase the hydrophilicity of our compounds; the benzyl units increase both their hydrophobicity and aggregation ability through π–π stacking interactions of the aromatic rings.[3]

Compounds **1–7** have triazole and benzene rings in common, but each differs in the length and position of its aliphatic chain. These small changes cause the different gelation properties of compounds **1–7**. Table 1 displays the water-gelating properties of compounds **1–7**. The gelation test was conducted as follows; The sample was heated in water until it dissolved and then it was

cooled to room temperature. The gelation ability was determined by a "stable-to-inversion-of-the-container" method.[9] As shown in Table 1, these compounds display quite different water-gelating properties. When the aliphatic chain is in the *para* position, the compound exhibits excellent water-gelation ability, but when it is in the *ortho* position, the compound's gelation ability is relatively poor. We do not observe a clear relationship between the length of the aliphatic chain and the gelation ability. It is not possible to arrive at an exact explanation of these results without X-ray crystal structure data, but we believe that some of the aliphatic chains may assist or interrupt the π–π stacking interactions sterically. Among the seven compounds, the *p*-ethylbenzyl derivative **6** is the best hydrogelator; it forms gels in water at concentrations as low as 0.2 wt%.

Fig. 1 displays SEM images of the hydrogels prepared in water from **1**, **4**, **6** and **7**. Two types of aggregation modes are observed: fibrous and lamellar. Only **6** exhibits a fibrous

Table 1 Gelation properties of **1–7** in pure water

Compound	State[a]	MGC[b]	MW
1	G	0.3	385.37
2	UG	3	399.40
3	UG	1	399.40
4	G	0.6	399.40
5	UG	2	413.43
6	G	0.2	413.43
7	G	0.8	441.48

[a] G: white opaque gel; UG: unstable, white opaque gel. [b] MGC: minimum gel concentration in wt%.
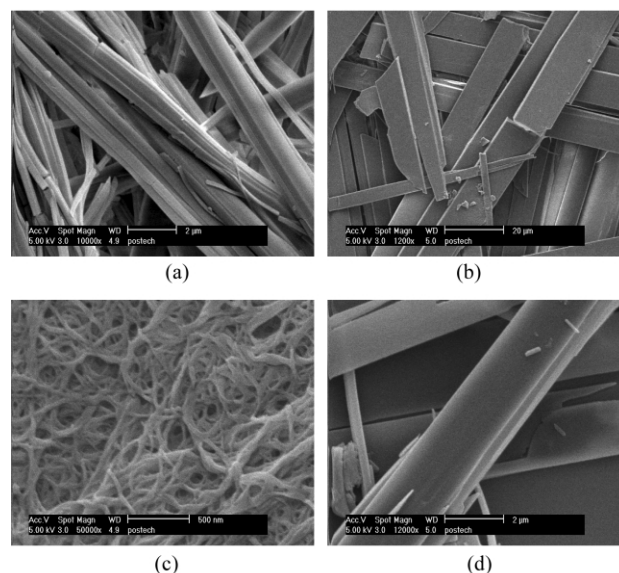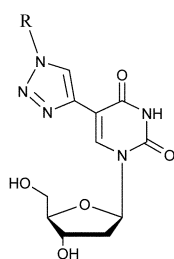

(a)   (b)

(c)   (d)

Fig. 1 SEM images of the hydrogels formed from water incorporating 1 wt% of compounds (a) **1** (scale bar is 2 μm), (b) **4** (scale bar is 20 μm), (c) **6** (scale bar is 500 nm) and (d) **7** (scale bar is 2 μm).

1. R = Benzyl
2. R = *o* - Methyl benzyl
3. R = *m* - Methyl benzyl
4. R = *p* - Methyl benzyl
5. R = *o* - Ethyl benzyl
6. R = *p* - Ethyl benzyl
7. R = *p* - Butyl benzyl

aggregated morphology. Fibrous structures can contain more solvent than can lamellar structures because of their greater void volumes. This rationale seems to explain why **6** is the best hydrogelator in this series. We obtained some more SEM images to investigate how the degree of aggregation depends on weight percentage of the gelator. Fig. 2 displays the effect of changing the weight percentage of **6**. At 2 wt%, the fibrous structure is more entangled than it is at 0.25 wt%. The SEM image at 0.25 wt% shows the coexistence of both entangled and disentangled fibres. Thus, at relatively low weight percentages of **6**, the fibre structure becomes looser and the gel stability is lower. In these SEM images, it is quite amazing that the microscopic aggregation structures are so different despite the small differences in their minimum gel concentrations.

We obtained FTIR spectra in order to understand the hydrogelators' modes of aggregation, because these spectra give useful information on intermolecular interactions. We collected data for compounds **1**, **4**, **6** and **7** in the gel and solid phases by preparing hydrogels in D_2O^4 and as pellets with KBr, respectively. All the samples in the gel phase display a common broad absorption band in the range 3100–3500 cm^{-1} (Fig. 3), which indicates that the driving force of hydrogelation with **1**, **4**, **6** and **7** is hydrogen bonding between the 3'- and 5'-OH groups of 2'-deoxyuridine. Significant differences between compounds are detected in the range of the amide absorption band (spectra not shown). Compound **6** presents absorption bands at 1701 and 1679 cm^{-1} in its FTIR spectrum in the solid phase. In the gel phase, however, the absorption bands shift to 1741 and 1697 cm^{-1}. The FTIR spectra of **7** in both phases display the same absorption bands at 1725 and 1695 cm^{-1}. These signals indicate that there are differences between the modes of hydrogen bonding at the carbonyl and NH functions of the two molecules in the gel phase.[10] These results suggest a reason why the *p*-
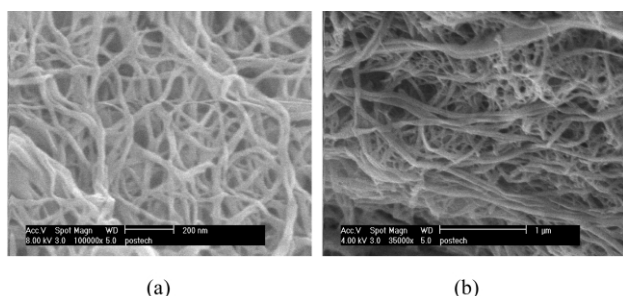

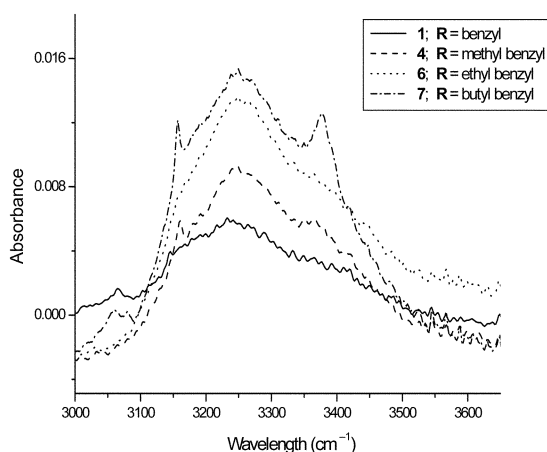**Fig. 2** SEM images of (a) 2 wt% **6** (scale bar is 200 nm) and (b) 0.25 wt% **6** (scale bar is 1 μm).

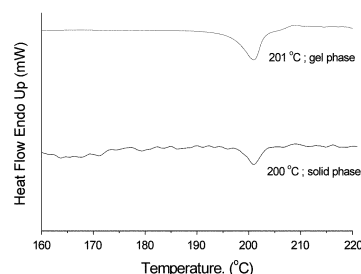**Fig. 3** FTIR spectra of **1**, **4**, **6** and **7** in the gel phase (D$_2$O).

Fig. 4 Differential scanning calorimeter diagram of **6**.

ethylbenzyl derivative's aggregation pattern is different from that of the others: the *p*-ethylbenzyl derivative undergoes additional hydrogen bonding interactions between nucleobase moieties, and this small change causes an aggregation pattern that results in a fibrous entangled network.

To study the thermal properties of the hydrogelators, we obtained data by differential scanning calorimetry (Fig. 4, only shown for **6**). The melting point peak of hydrogelator **6** is 200 °C in the solid phase ($\Delta H = 9.1$ kcal mol^{-1}) and 201 °C in the gel phase. The enthalpy value and melting point peak in the solid phase of hydrogelator **1** are 12.2 kcal mol^{-1} and 205 °C, respectively. These results indicate that these hydrogelators have good thermal stability and form solid-like hydrogels in water.

In summary, we have prepared the first low-molecular-weight hydrogelators based on 2'-deoxyuridine. These hydrogelators self-assemble through hydrogen bonding interactions and display aggregation properties that depend on the nature of these hydrogen bonds.

Notes and references

† Synthesis of hydrogelators: 5-iodo-2'-deoxyuridine was protected at its 5'-OH group using the 4-monomethoxytrityl (MMTr) group and then acetylene formation was performed by the Sonogashira coupling method with trimethylsilylacetylene. The trimethylsilyl group was deprotected using tetrabutylammonium fluoride in THF. Using the Sharpless cycloaddition method, the triazole ring was then formed.[11] The MMTr group was then deprotected using AcOH in CH$_2$Cl$_2$.

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