Water gelation abilities of alkylbenzyltriazole-appended 2′-deoxyribonucleoside and ribonucleoside†

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Alkylbenzyltriazole units covalently bonded onto uridine nucleosides were synthesized and their suitability for water gelation compared with 2′-deoxyuridine derivatives was tested.

Various types of small molecule-based gelators of organic and aqueous solvents have been investigated to determine their essential characteristics for gelation.[1] These systems, which have been prepared from amino acids,[2] bis-ureas,[3] sugars,[4] nucleic acids,[5,6] and steroids,[7] are designed to self-assemble through aggregation mediated by hydrophobic, dipole–dipole, van der Waals, π–π, and hydrogen bonding interactions.[1] For the small molecule hydrogelators in particular, the balance between their hydrophilic and hydrophobic characteristics and the nature of the gelators' interactions with water are important factors.[8] Hydrogels are receiving an increasing amount of attention from both academia and industry because of their potential applications[9] and, therefore, it remains necessary to establish the design rules for preparing hydrogelators effectively.

We are interested in developing chemically modified nucleoside-based hydrogelators that will behave as delivery systems. Although a few examples of nucleic acid-based hydrogelators are known, they do not appear to follow any common design rules.[5a,6] In this paper, we report the preparation of effective hydrogelators based on nucleobase-modified uridine and describe how the gelation properties depend crucially on the nature of a single hydroxyl group.

In a previous paper,[5a] we reported that the alkylbenzyl triazole-appended 2′-deoxyuridines **1a–d** form gels in water; the best gelator of that series was the ethylbenzyltriazole-appended 2′-deoxyuridine **1c**. In this study, we investigated the corresponding series of uridine derivatives, *i.e.*, systems that exhibit one extra hydroxyl group and, therefore, possess somewhat increased hydrophilicity (Fig. 1). We introduced the same appending units, alkylbenzyltriazole groups, to compare how the hydrophilic/hydrophobic balance affects each system. We synthesized the four nucleosides by modifying the 5-position of the uracil base with alkylbenzyltriazole units using methods similar to those we described previously (Scheme 1).[5a]

As expected, the uridine-based hydrogelators exhibited gelation behavior different to that of the corresponding 2′-deoxyuridine-based systems. In general, they possessed relatively higher minimum gelation concentrations (MGCs), with three of them (**2a–c**) forming unstable partial gels in water (Table 1); in addition, these systems required more than 5 min to establish hydrogelation.

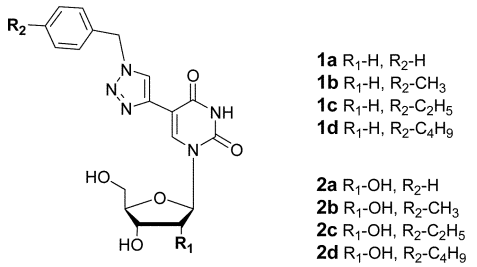
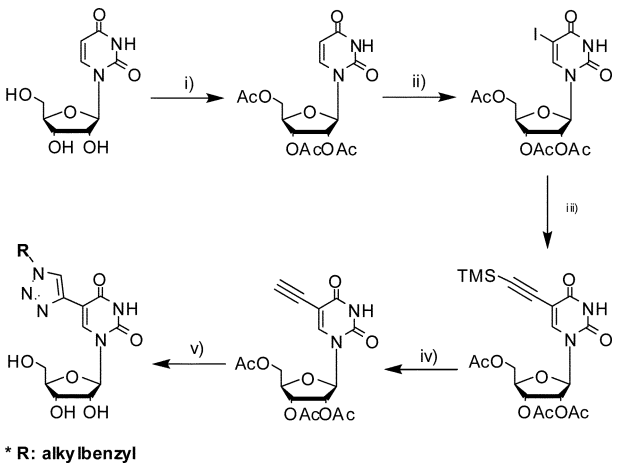


Fig. 1 2′-Deoxyuridine (**1a–d**)- and uridine (**2a–d**)-based hydrogelators.



Scheme 1 Synthesis of alkylbenzyltriazole-appended uridines. *Reagents and conditions*: (a) acetic anhydride, triethyl amine, 1,4-dioxane, rt; (b) iodine, ammonium cerium(IV) nitrate, MeCN, 80 °C, 1 h; (c) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, CuI, triethylamine–THF (3 : 1), 45–50 °C; (d) TBAF, THF, rt; (e) 1. alkylbenzylazide, Na-ascorbate, $CuSO_4 \cdot 5H_2O$, *tert*-BuOH–H_2O (1 : 1), rt, 2. K_2CO_3, MeOH–H_2O (1 : 1), rt.

Table 1 Gelation properties of **1a–d** and **2a–d** in water at room temperature[a]

	1	2
a	G (0.3)	UG (2.5)
b	G (0.6)	PG (4.0)
c	G (0.2)	PG (4.0)
d	G (0.8)	G (1.0)

[a] G: Stable gel; UG: unstable gel; PG: partial gel. Minimum gelation concentrations (MGCs) are provided in parentheses (wt%).

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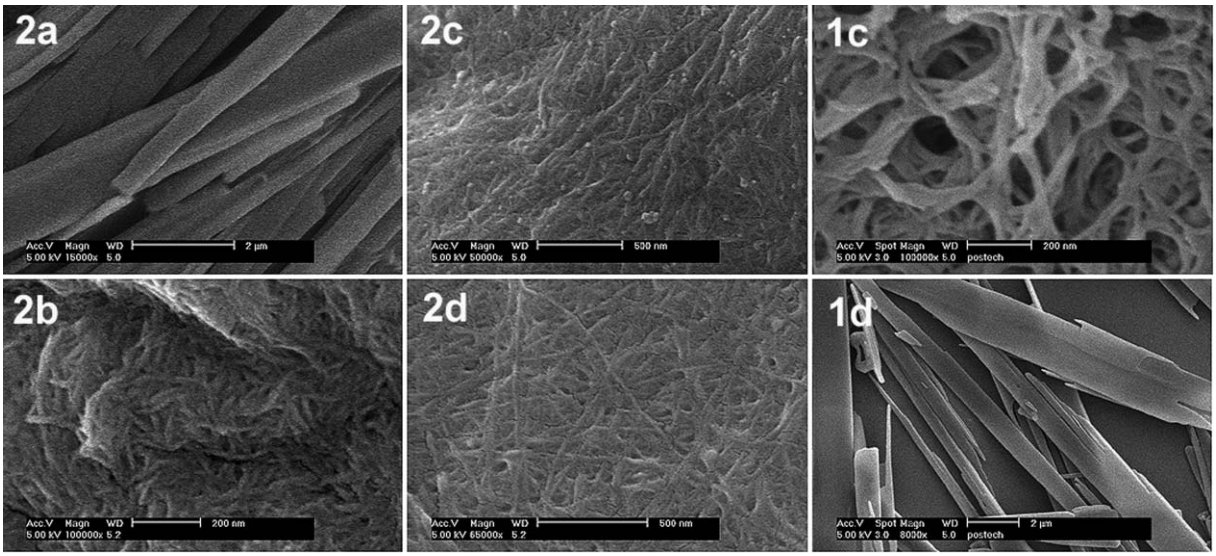

Fig. 2 SEM images of the xerogels formed from hydrogels. The white scale bars are 2 μm long in **2a** and **1d**, 200 nm long in **2b** and **1c**, and 500 nm long in **2c** and **2d**.

The hydrogels formed by the modified uridines were less opaque than those of 2′-deoxyuridine-based hydrogelators despite their higher MGCs. Compound **2a** began to precipitate from the gel after 1 h; of this series of uridine-derived compounds, **2d** formed the most stable hydrogel and had the lowest MGC. We used scanning electron microscopy (SEM) to examine the nano- or meso-scale structures of these uridine-based hydrogels. Fig. 2 displays the SEM images of the xerogels (freeze-dried gels) prepared from the hydrogels. Interestingly, the xerogels formed from **2b** and **2d** had fibrous morphologies, unlike the lamellar structures observed for their corresponding 2′-deoxyuridine-based congeners. With the exception of the xerogel prepared from **2a**, these systems all possessed more densely intertwined, but thinner, nanofibers (the individual fibers had diameters of *ca.* 10–30 nm) than we had observed previously (note in Fig. 2 that the xerogel prepared from **1c** possesses nanofibers having an average diameter of *ca.* 30–50 nm).

To evaluate the different gelation behavior in more detail, we measured the FTIR spectra of the gel and solid phases of the four compounds that exhibited the best gelation ability, namely the pairs of ethylbenzyltriazole- and butylbenzyltriazole-substituted systems. We carefully monitored the signals in the FTIR spectra in the range of 1500–1700 and 3000–3500 cm^{-1}; Table 2 summarizes the results.

Table 2 Wavenumbers (cm^{-1}) for the IR absorption signals of the hydroxyl groups and amide I & II bands

		Hydroxyl group	Amide I band	Amide II band
1c	KBr	3452	1680	1543
	Gel	3250	1697	1542
1d	KBr	3477	1647	1511
	Gel	3250	1695	1542
2c	KBr	3352 (br)	1650	1515
	Gel	3394 (br)	1652	1540
2d	KBr	3350 (br)	1650	1511
	Gel	3394 (br)	1653	1541

The peaks in the wavenumber range from 1500 to 1700 cm^{-1} represent the amide I and amide II bands. For **2c**, **2d**, and **1d**, the wavenumbers of both of these bands increased upon proceeding from the solid phase to the gel phase. This finding indicates a change in the hydrogen bonding pattern—namely stronger and weaker hydrogen bonds for the carbonyl and NH units, respectively, in the gel phase.[10] In the case of **1c**, however, the wavenumber of the amide I band increased while that of the amide II band decreased slightly, suggesting that the hydrogen bonding interactions of the carbonyl and NH units were the main interactions in both phases.

We monitored the hydrogen bonding of the hydroxyl groups by observing their peaks in the range 3000–3500 cm^{-1}. The signals for the hydroxyl groups of hydrogelators **2c** and **2d** were much broader in both the gel and solid phases relative to those of **1c** and **1d**. Because the uridine-based hydrogelators in series **2**, both have an additional hydroxyl group in their sugar moieties, it is not surprising that they would be more hydrophilic (*i.e.*, interact to a greater degree with water molecules) than the compounds in series **1**.

The FTIR spectroscopic signals correlate with the values of MGC and the stabilities of the hydrogels. For example, the best hydrogelator, compound **1c**, exhibited a different signal pattern for its amide I and II bands; both the carbonyl and NH moieties of the uracil base participated in intermolecular hydrogen bonding interactions. In the cases of **2c**, **2d** and **1d**, however, only the carbonyl moieties took part in hydrogen bonding interactions. That is to say, hydrogelator **1c** self-assembled into fibers through the action of its additional hydrogen bonding unit; its balance between hydrophilicity and hydrophobicity in water resulted in the formation of a stable hydrogel. Although the NH moieties of the hydrogelators **2c** and **2d** were not involved in hydrogen bonding, these compounds possess the additional hydroxyl group, which enables favorable additional intermolecular interactions. As a result, they also exhibited fibrous self-assembled microstructures in their SEM images. Nevertheless, the presence of the additional hydroxyl group results in these compounds interacting to a greater extent with the solvent (water).

Therefore, most of the uridine-based hydrogelators did not form stable hydrogels. Of the uridine-based hydrogelator systems, the best balance of hydrophilicity and hydrophobicity—*i.e.*, the best gelation behavior—was that of compound **2d**; the extra hydrophilicity imparted by the additional hydroxyl group in the sugar moiety was offset by the hydrophobicity of the butylbenzyl group in the base moiety to provide the most effective hydrogelation. The validity of this design rule is presently under further investigation.

In summary, we have studied the properties of new uridine-based hydrogelators in comparison with their 2′-deoxyuridine-based congeners, which we had reported previously. As expected, these two series of nucleoside-based gelators displayed different gelation properties. For example, the butylbenzyltriazole-appended hydrogelator **2d** was the most effective gelator of the uridine series, but its mode of self-assembly leading to hydrogelation was different from that of the ethylbenzyltriazole-appended hydrogelator **1c**, the best system among the 2′-deoxyuridine series.

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