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Novel thymidine-based organogelators and their gelation behaviours

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We report on a synthesis of novel thymidine based organogelators and a study of their gelation types in relation to structure and solvent, using various data acquired through FT-IR, SEM images and differential scanning calorimetry.

Gelation of organic solvents by low molecular mass compounds has received increasing attention in recent years.[1] There are several examples of organogel formation by prebiotic molecules such as amino acid derivatives,[2] dipeptides,[3] and carbohydrates.[4] We have envisioned that nucleosides are promising building blocks for new gelators and herein report on the design and synthesis of novel nucleoside-based organogelators and their gelation behaviours.

The starting nucleoside, thymidine, consists of hydrophilic sugar parts and thymine nucleobase which has hydrogen bonding capability. We employed four different linking units (urea, amide, carbamate, and ester) and 3′-*N*-alkylation for the attachment of alkyl groups. In some cases, bulky silicon group at the 3′-position was introduced for better solubility. As a result, we finally synthesized compounds **1**–**5** as thymidine based organogelators (Fig. 1).†

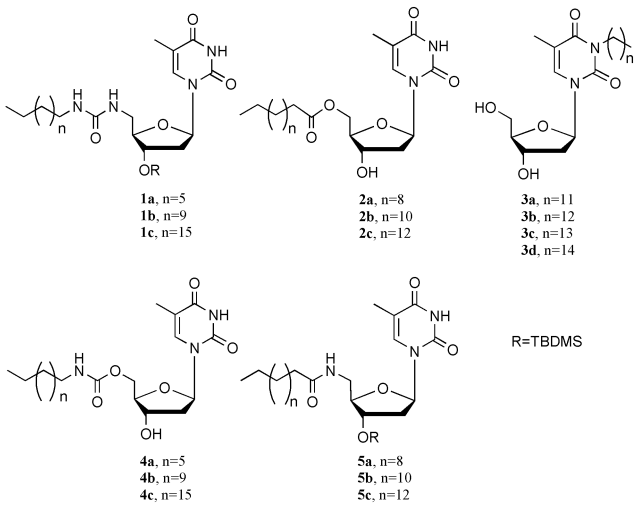

Fig. 1 Five types of thymidine–based organogelator.

In the gelation test conducted with organogelators, the gel formation of these compounds with organic liquids was determined by a 'stable to inversion of the container' method using around 20 organic liquids. Cyclohexane, n-pentane, n-hexane, and n-heptane were suitable organic liquids in forming robust and translucent gels with the urea- and amide-linked gelators. For the carbamate- and ester-linked gelators, toluene, 1,2,3,4-tetrahydronaphthalene (THN), propylene carbonate and 3-methoxypropionitrile were appropriate organic liquids in producing opaque gels. 3′-*N*-alkylated gelators formed opaque gels in benzene, CCl_4, THN, toluene, methylene chloride, cyclohexane and n-hexane. Gels were not observed in methanol, ethanol, chloroform, tetrahydrofuran, ethyl acetate, acetone, diethyl ether, 2-propanol and 2-octanol. Most of our products were gelated at a gelator concentration of 2.0 wt% (Table. 1).

To gain visual insights into the aggregation mode, a dry sample for SEM studies[5] was prepared (Fig. 2) and three different gel structures were observed with SEM: (i) fibrous structure in urea-linked gelator/cyclohexane and 3′-*N*-dodecylthymidine/CCl_4, (ii) woven structure in amide-linked gelator/octane, and (iii) lamellar structure in ester-linked gelator/toluene and in 3′-*N*-dodecylthymidine/toluene, benzene and THN. The difference in the organogelators' gelation ability is attributed to the formation of mutually exclusive gel networks caused by intermolecular hydrogen-bonding interactions.

In the FT-IR spectra of 3′-*N*-alkylated thymidine, the difference between the solid and the gel phase could be detected clearly. In solid phase, a hydrogen-bonded OH peak was not observed, but it was in the gel phase. If the OH group undergoes hydrogen bonding, the peak of free OH group ($\sim$3600 cm^{-1}) shifts to lower frequency (3400–3300 cm^{-1}). As shown in Fig. 3, gel solutions gave only broad peaks in the range 3400–3500 cm^{-1}. Thus, these FT-IR results indicate that intermolecular hydrogen-bonding interaction is one of the driving forces for the formation of the gel network. In addition, gel formation is affected by solvent systems.[6] In the SEM images of **3b**, a lamellar type was observed in THN, but a fibrous type was observed in CCl_4. These phenomena can be explained by a solvent dependence of gel formation. Usually lamellar type gels were observed in aromatic solvents such as THN, toluene, and benzene. By changing gelation solvents, gels aggregated in a different pattern due to differences in hydrogen bonding interaction, van der Waals interaction, and π–π stacking. These

Table 1 Gelation test of **1**–**5** (2wt%)[a]

Organic solvent	**1a**	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**	**3d**	**4a**	**4b**	**4c**	**5a**	**5b**	**5c**
Benzene	P	P	—	G	pG	G	P	G	G	G	Ins	Ins	Ins	S	S	S
Toluene	P	P	Ins	G	G	G	P	G	G	—	Ins	pG	G	S	S	S
CCl_4	S	P	—	Ins	G	G	G	—	—	—	Ins	Ins	Ins	—	—	—
THN	—	—	—	pG	G	G	G	pG	pG	O	G	G	G	—	—	—
n-Hexane	G	G	G	Ins	pG	G	—	—	—	—	Ins	Ins	Ins	G	G	G
Cyclohexane	G	G	G	Ins	pG	G	—	—	—	—	Ins	Ins	Ins	G	G	G
n-Pentane	G	G	G	—	—	—	—	—	—	—	—	—	—	G	G	G
n-Heptane	pG	G	G	—	—	—	—	—	—	—	—	—	—	G	G	G
n-Octane	P	pG	G	—	—	—	—	—	—	—	—	—	—	G	G	G

[a] Ins = insoluble; pG = partial gel; G = gel; P = precipitation; S = soluble; O = oilic; only nine common gelating solvents are listed here.

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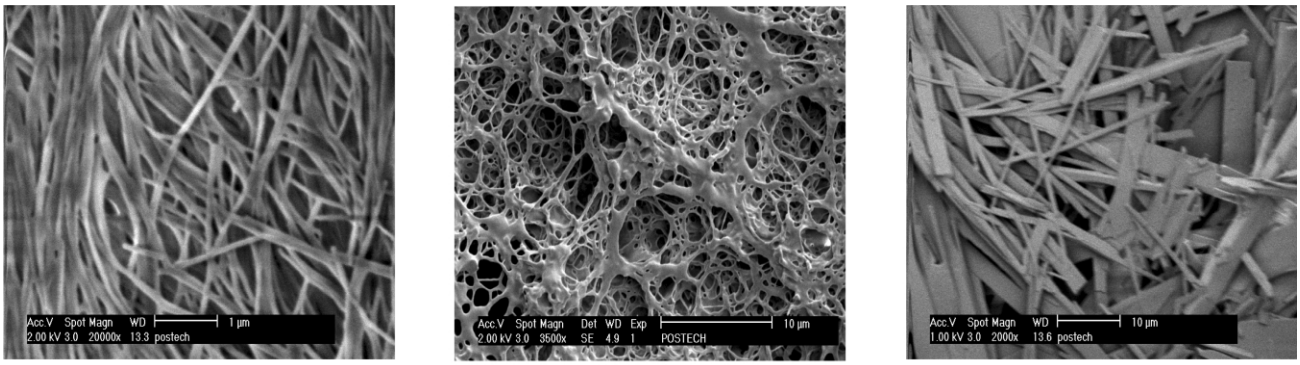

(a) (b) (c)

Fig. 2 SEM images of **3** and **5**; (a) **3a**/CCl_4 system, (b) **5c**/octane system, (c) **3c**/toluene system. The different gelling abilities are attributed to differences in hydrogen bonding interactions.

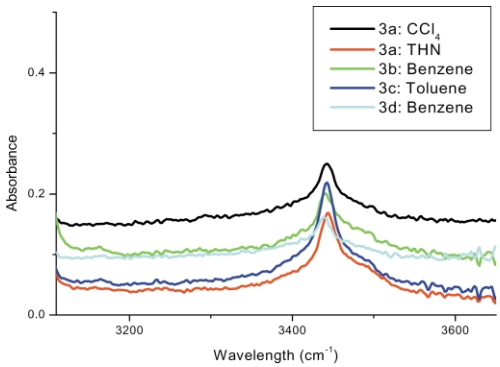

Fig. 3 FT-IR spectra of 3′-*N*-alkylated thymidine, **3a**–**3d.**

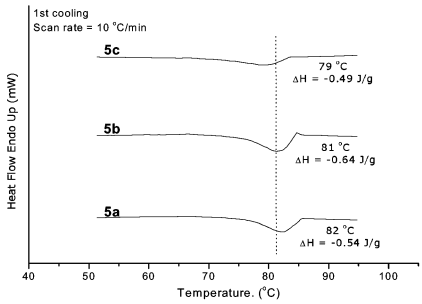

Fig. 4 Differential scanning calorimeter diagram of **5**.

ideas are also applicable to the cases of urea-, amide-, carbamate-, and ester-linked organogelators.

The differential scanning calorimeter experiment (Fig. 4) with **5** showed that the gelation temperatures of **5a**–**5c** are in the range of 82–79 °C and the temperature of gelation became lower as the alkyl chain became longer.[7] Because of the hydrophobic interactions between the long alkyl chains, aggregation occurred more easily.

In conclusion, we have demonstrated for the first time that it is possible to design the synthesis of novel thymidine-based gelators by simple modification of the sugar and base parts. Thymidine provides promising building-blocks for new gelators with different gelation abilities and a different three-dimensional network structure. With these results, a study is currently in progress on the design of nucleoside based hydrogelators, which may have potential applicability in biosystems.

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Notes and references

† For the synthesis of the desired compounds **1** and **5** from thymidine, functional group transformation of 5′-OH to the iodide and protection of 3′-OH with the *tert*-butyldimethylsilyl (TBDMS) group was carried out. This was followed by the azide formation with sodium azide in *N*,*N*-dimethylformamide (DMF). The 5′-azido thymidine compound was prepared by this procedure. Reduction of this azido compound to the desired 5′-amino intermediate was carried out by using hydrogen gas in the presence of Pd/C catalyst. Urea-linked gelators **1** were prepared by treating the corresponding alkyl isocyanates and amide-linked gelators, **5** were prepared with alkylic acids under the conditions with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)/4-dimethylaminopyridine (DMAP). Carbamate-linked gelators **4** were prepared by the regioselective addition of alkyl isocyanate at the 5′-OH. Ester-linked gelators **2** were prepared by the following steps: protection of 5′-OH with 4,4′-dimethoxytrityl (DMTr) group, protection of 3′-OH with phenoxy acetyl group, and deprotection of DMTr group. 3′-*N*-alkylated thymidine gelators **3** were prepared by the treatment of alkyl halide and sodium hydride in DMF.

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