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Organogels of a nucleobase-bearing gelator and the remarkable effects of nucleoside derivatives and a porphyrin derivative on the gel stability

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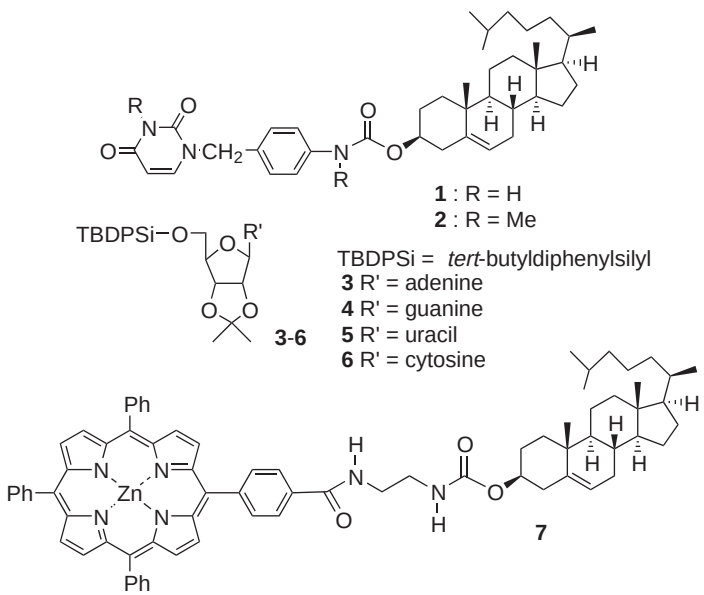
Abstract—An organogelator, which has a nucleobase group at its terminus, features one-dimensional, cholesteric-helical organization: the gel was remarkably destabilized by the addition of nucleoside derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

The focus in supramolecular chemistry is mainly on organizing monomeric species in a desired superstructure. One of the new fields of supramolecular chemistry currently receiving attention is that of the gelators,[1] low molecular weight molecules capable of immobilizing a liquid. Gel formation has been used as a tool to easily organize monomeric species into complex higher-order structures, such as fibrous, tubular and helical structures.[1–5] Although it has so far been proven impossible to predict the gelation ability of a particular compound, cholesterol-derivatives have been shown to be excellent gelators. Moreover, they frequently exhibit a character-



Scheme 1.

Keywords: supramolecular chemistry; gels; nucleobases.

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Table 1. Gelation temperatures (T_{gel}) of compounds **1** and **2** in cyclohexane and of mixtures of compounds **1** and **3** (concentration of **1** is 7.94 mmol dm^{-3} in cyclohexane). T_{gel}'s were determined of samples in a sealed vial, allowing measurements above the boiling point of cyclohexane (80.7°C)

1 (mmol dm^{-3})	T_{gel} (°C)	**2** (mmol dm^{-3})	T_{gel} (°C)	Ratio **3/1**	T_{gel} (°C)
4.13	80	9.13	30	0	123
4.76	94	10.6	33	0.20	93
5.56	100	12.2	35	0.38	72
6.35	104	13.7	38	0.50	75
7.14	111	15.2	39	0.59	51
7.94	123			0.69	48
				0.82	27

istic helical structure in its gel-fibers.[2,5] It thus occurred to us that forming a gel with a gelator, which has a cholesterol as well as a nucleobase unit, would be an ideal way to form a one-dimensional helically organized structure with a nucleobase group at its terminus. In this facile and novel way a DNA-type structure would be obtained with the possibility to study this newly designed system for DNA-mimetic properties. To realize this idea, we initially designed and synthesized compound **1** (see Scheme 1) and studied the gels it forms.[6]

The solvents in which compound **1** formed a gel were benzene, toluene, *p*-xylene, *n*-butanol, *n*-octane, and cyclohexane (all at 15.9 mmol dm^{-3}). For the subsequent studies, cyclohexane was used as a solvent. Firstly, the gelation temperature (T_{gel}) has been determined of gels with various concentrations of compound **1** (Table 1) to estimate the strength of the gel. As can be seen, very strong gels are formed; when the T_{gel} values were evaluated in a sealed tube, they were even higher than the boiling point of cyclohexane (80.7°C).

Ideally, compound **1** forms a one-dimensional array with its uracil moieties sticking out side-ways in such a way that it is able to exhibit recognition of the complimentary base, i.e. adenine. Alignment of the adenine moiety would result in an increase in the π-area and thus increase the π–π stacking, and increase the gel stability just as a double helix of nucleic acids is stabilized.[7] To test whether this has been accomplished in our system, we gelated compound **1** in the presence of additives **3**–**6**, derivatives of nucleosides, and measured the T_{gel} of the resulting gels. The results are presented in Fig. 1. Surprisingly, even a small amount of additive results in weakening of the gels. Especially, the presence of guanosine derivative **4** has a very pronounced effect as 0.01 equivalents already reduce the T_{gel} with 92°C, and gels can only be obtained in the presence of less than 0.05 equivalents of **4**. Apparently, the uracil moiety forms intergelator hydrogen bonds, the formation of which is disturbed by the presence of hydrogen bond forming additives, especially compound **4**, which can form the most hydrogen bonds. Nucleic acids can enjoy increased stability by π–π stacking in a double helix, because both parts are polymers with each unit acting cooperatively, and thus resulting in an overall stabilizing effect. In our case the gel fiber can be viewed as polymer-like, however, the additives are monomeric units, thus not acting cooperatively, and therefore, formation of hydrogen bonds with the gelator only results in weakening of the gel.

One characteristic of DNA is that flat compounds with a large π-area are able to intercalate, and one example of such compounds is porphyrine. We therefore gelated compound **1** (7.94 mM in cyclohexane) in the presence of porphyrine derivative **7**.[8] We found that a gel was formed only when less than 0.4 equivalents of compound **7** was present. Subsequently, we measured the CD spectrum of a gelated sample of **1** (see Fig. 2) in the presence of 0.2 equivalents of **7**. Comparison of the spectrum with the CD-spectrum of just **7** at the same concentration showed an induced CD-signal in the Soret region, showing that a signal in this region of the

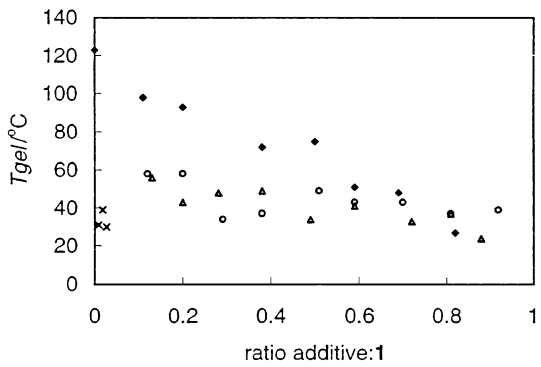

Figure 1. T_{gel} of gels formed by **1** in cyclohexane in the presence of additives, **3** (◆), **4** (×), **5** (○) and **6** (△).

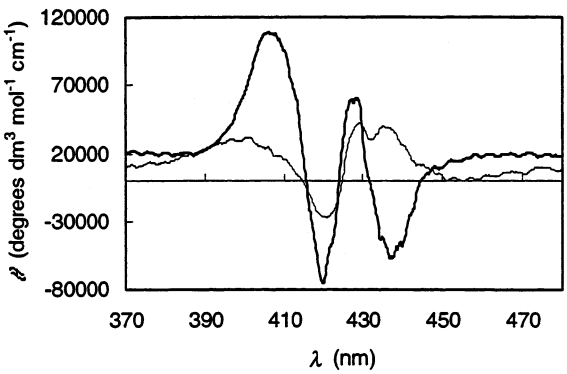

Fig. 2. CD-spectra of gelated sample of **1** (7.94 mmol dm^{-3} in cyclohexane), **7** (1.74 mmol dm^{-3}) (bold line), and of **7** (1.74 mmol dm^{-3}) (thin line).

CD-spectrum is induced by the gelation with **1**, and suggesting that **7** is incorporated into the gel fiber.

The foregoing findings indicate that added nucleoside derivatives and intercalator exert a conspicuous influence on the gel stability, probably because of disruption of intergelator hydrogen bonds. In order to substantiate the importance of intergelator hydrogen bond formation for the gel strength, gelation studies were carried out with reference compound **2**, which lacks hydrogen-bonding donor sites.[9] As expected, the gelation ability of this compound in cyclohexane proved to be strongly reduced. As shown in Table 1, the T_{gel} values for **2** are lower by about 60°C than those for **1**, even though the used gelator concentrations are much higher. Compound **2** was also gelated (15.2 mmol dm^{-3} in cyclohexane) in the presence of compound **3** as an additive. However, in this case there is no decrease in T_{gel} observed with increasing amount of compound **3**,[10] thus proving that hydrogen bonding between the gelator molecules of compound **1** substantially contributes to the stability of the gels it forms. Proof for the existence of intergelator hydrogen bonds was obtained by measuring the ^{1}H NMR spectra of **1** at different concentrations in $CDCl_3$. The same technique was used to investigate whether **1** forms hydrogen bonds with additive **3**. The results are summarized in Table 2. Apparently both NH-groups are involved in intergelator hydrogen bonds as both chemical shifts shift upfield in more dilute samples. More interestingly, addition of **3** only affects the chemical shift of the uracil-NH, shifting it downfield, suggesting that the adenine moiety of **3** only forms hydrogen bonds with the uracil moiety of **1**. These results are further evidence that the uracil moiety of **1** forms intergelator hydrogen bonds in the gel phase, which are disrupted when additive **3** is added.

In order to get a better insight into the aggregation mode of the gelator molecules, CD spectroscopy was used to observe the spectroscopic effects accompanying the gel to sol phase transition. The CD spectra of a gelated sample of **1** (4.13 mmol dm^{-3}) and of **2** (9.13 mmol dm^{-3} in cyclohexane) were recorded at various temperatures. The molar ellipticities at the absorbance maximum (between 259 and 260 nm) are plotted in Figures 3 and 4, respectively. From these figures it can be seen that **2** has a much higher molar ellipticity than **1**, which suggests a higher stacking mode of the uracil moieties of **2** in the gel phase. A drastic decrease in CD

Table 2. Chemical shifts of the carbamate-NH (indicated as NH1) and the uracil-NH (NH2) of **1** at different concentrations and in the presence of **3**

1 (mmol dm^{-3})	**3** (mmol dm^{-3})	δ_{NH1} (ppm)	δ_{NH2} (ppm)
31.72	–	6.771	8.825
15.86	–	6.685	8.506
3.172	–	6.592	8.056
2.855	2.855	6.602	8.576
2.617	5.287	6.609	8.907

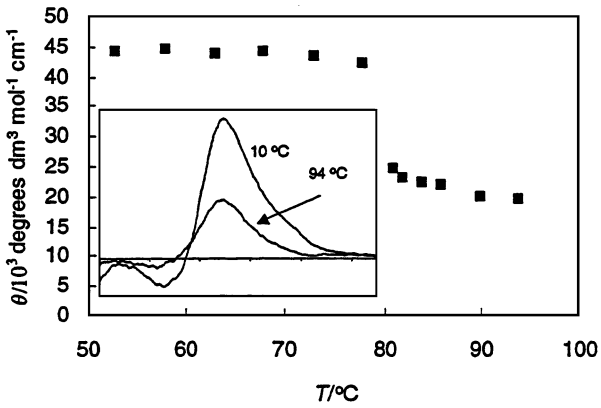

Figure 3. Molar ellipticity at 259.8 nm of a gelated sample of compound **1** (4.13 mmol dm^{-3} in cyclohexane; 0.01 cm cell width) as a function of temperature. Inset: two CD-spectra, one recorded at 10°C (θ_{max} = 259.6 nm) and one at 94°C (θ_{max} = 259.4 nm); horizontal axis: λ (nm), plot limits: 320 and 210 nm; vertical axis: θ (degrees dm^3 mol^{-1} cm^{-1}), plot limits: −12 000 and 50 000 degrees dm^3 mol^{-1} cm^{-1}.

intensity between 78 and 81°C in the CD-spectra of **1** can be ascribed to a gel to sol transition as it is in perfect agreement with the T_{gel} measured for this concentration (see Table 1). Above 81°C the sample is still CD-active, although much weaker than below 81°C (see inset in Fig. 3), indicating that molecular aggregation exists above T_{gel} although this aggregation is not strong enough to gelate the solvent. For compound **2** again a phase transition could be observed in the CD spectra as the molar ellipticity drops from 9.4×10^4 degrees dm^3 mol^{-1} cm^{-1} at 24°C to 2.2×10^3 degrees dm^3 mol^{-1} cm^{-1} at 32°C (T_{gel} measured for this concentration was 30°C). One difference in the Variable Temperature-CD spectroscopy of compound **2** compared to that of compound **1** is that the CD activity reduces to minimal proportions above T_{gel} in the former case (see inset in Fig. 4). Apparently, compound **2** completely dissolves

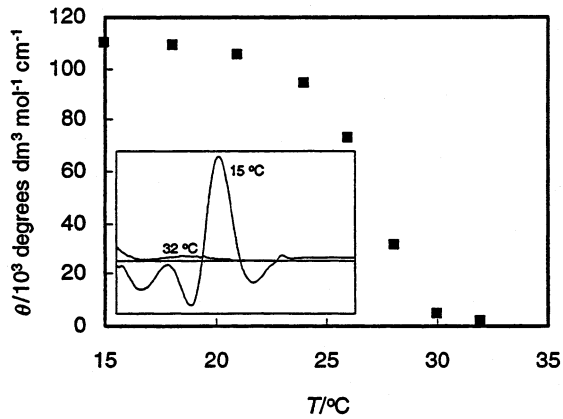

Figure 4. Molar ellipticity at 256.6 nm of a gelated sample of compound **2** (9.13 mmol dm^{-3} in cyclohexane; 0.01 cm cell width) as a function of temperature. Inset: two CD-spectra, one recorded at 15°C (θ_{max} = 256.8 nm) and one at 32°C; horizontal axis: λ (nm), plot limits: 320 and 210 nm; vertical axis: θ (degrees dm^3 mol^{-1} cm^{-1}), plot limits: −60 000 and 120 000 degrees dm^3 mol^{-1} cm^{-1}.

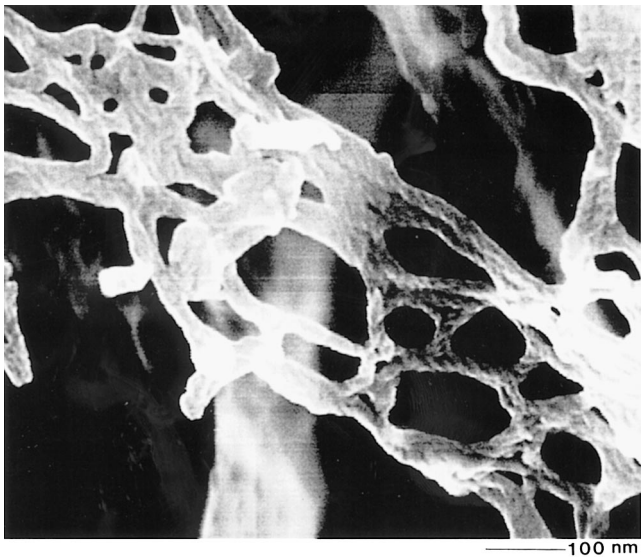

Figure 5. SEM picture of a xerogel of compound **1** (7.94 mmol dm^{-3} in cyclohexane).

above its T_{gel}, whilst compound **1** can still be aggregated through hydrogen bonds at a temperature above T_{gel}.

The CD spectra suggest that the gelator molecules of compound **1** are arranged in a helical structure in the gel phase. To further corroborate this, scanning electron microscopy (SEM hereafter) pictures were taken of a xerogel of **1** in cyclohexane, and Fig. 5 shows a characteristic SEM picture. One can recognize a well-developed network structure consisting of fibrils with diameters of 20–40 nm in width. At several positions the fibrils show a helical structure, which may be related to the strong CD intensity of **1** in the gel phase, and apparently they are right-handed.

In this study we have synthesized compound **1**, a nucleobase-bearing organogelator, and have shown with CD spectroscopy and SEM that it forms helical gel fibers in the gel phase and the gel stability is sensitively affected by addition of nucleoside derivatives and intercalators. Further functionalization of the gelator towards the development of non-covalently bonded polynucleotide mimics, which may directly interact with polynucleotides, is currently being carried out.

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6. Compound **1** was synthesized in 20% overall yield, starting from uracil. Analytical data for **1** (recrystallized from acetone): mp 243–245°C; found: C 73.95; H 8.72; N 6.57. $C_{39}H_{55}N_3O_4$ requires C 74.37; H 8.80; N 6.67%; δ_H (300 MHz, $CDCl_3$): 8.65 (1H, s, N*H*), 7.40 (2H, d, *J* 8.4, Ar-*H*), 7.24 (2H, d, *J* 8.7, Ar-*H*), 7.14 (1H, d, *J* 7.8, H_6 uracil), 6.73 (1H, s, N*H*), 5.68 (1H, d, *J* 7.8, H_5 uracil), 5.40 (1H, d, *J* 5.1, H_6 cholesteryl), 4.85 (2H, s, benzyl CH_2), 4.61 (1H, m, OC*H* cholesteryl), 2.39, 1.91 and 1.64–0.85 (43H, m, cholesteryl-*H*); δ_C (75 MHz, THF-d_8): 164.0, 153.7, 152.1, 144.8, 140.8, 140.5, 131.3, 129.5, 123.1, 118.9, 102.4, 74.7, 57.7, 57.1, 51.1, 50.8, 43.1, 40.7, 40.4, 39.4, 37.9, 37.4, 37.1, 36.8, 32.8, 32.8, 29.1, 29.0, 28.9, 25.1, 23.2, 22.9, 21.9, 19.7, 19.2, 12.2; *m*/*z* (-FAB) 629 (M–H), 628 (M–2H), 517 (M–uracil–H), 111 (uracil–H).
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9. Compound **2** was synthesized by reacting compound **1** with sodium hydride and methyliodide in DMF, yield: 67%. Analytical data for **2** (recrystallized from methanol): mp 162–163°C; found: C 74.88; H 9.08; N 6.38. $C_{41}H_{59}N_3O_4$ requires C 74.85; H 9.04; N 6.39; δ_H (300 MHz, $CDCl_3$): 7.26 (4H, s, Ar-*H*), 7.17 (1H, d, *J* 8.1, H_6 uracil), 5.76 (1H, d, *J* 7.8, H_5 uracil), 5.37 (1H, d, *J* 5.1, H_6 cholesteryl), 4.92 (2H, s, benzyl CH_2), 4.56 (1H, m, OC*H* cholesteryl), 3.37 (3H, s, NCH_3), 3.29 (3H, s, NCH_3), 2.36, 1.90 and 1.63–0.85 (43H, m, cholesteryl-*H*); δ_C (75 MHz, $CDCl_3$): 162.8, 154.7, 151.6, 143.4, 141.3, 139.4, 132.0, 128.1, 125.5, 122.3, 101.7, 75.4, 56.4, 55.8, 51.6, 49.7, 42.0, 39.4, 39.2, 38.2, 37.0, 36.7, 36.3, 35.9, 35.5, 31.6, 31.6, 28.0, 27.8, 27.7, 27.7, 24.0, 23.5, 22.6, 22.3, 20.8, 19.1, 18.4, 11.6; *m*/*z* (-SIMS) 656 (M–H), 655 (M–2H).
10. T_{gel}'s of compound **2** (15.2 mmol dm^{-3} in cyclohexane) in the presence of compound **3** (0, 0.2, 0.8 and 1.0 equivalents) were 39, 36, 32 and 35°C, respectively.