Molecular Design of "Super" Hydrogelators: Understanding the Gelation Process of Azobenzene-Based Sugar Derivatives in Water

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ABSTRACT
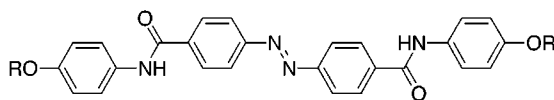
1 : R = β-D-glucopyranoside
2 : R = α-D-glucopyranoside
3 : R = α-D-galactopyranoside
4 : R = α-D-mannopyranoside

As an attempt to rationally design aqueous organogelators, a bolaamphiphilic azobenzene derivative (1) bearing two sugar groups was synthesized. Compound 1 formed a gel in water even at concentrations as low as 0.05 wt % (0.65 mM). Spectroscopic studies and electron-micrographic observations have clarified the gel structure and the origin of the gelation ability for water.

Organogels are thermoreversible, viscoelastic materials consisting of low molecular weight compounds self-assembled into complex three-dimensional structures.[1] Multiple noncovalent interactions such as hydrogen bonding, donor−acceptor, and hydrophobic interactions between the organogel building blocks, are responsible for the gel-forming process. Although many examples of gelators for organic solvents have been reported in the literature,[1] fewer studies on gelators for water (hydrogelators) have been presented.[2] The development of strong, thermoreversible hydrogelators can lead to useful new materials for drug delivery, wound healing, and tissue engineering processes.[3] Our group has synthesized and studied a variety of sugar-based compounds that are able to gelate water, organic solvents, or both.[4] We as well as others have noticed that hydrophobic interactions, for example, in the form of aromatic $\pi-\pi$ stacking, are indispensable for the formation of oriented aggregates in water and are most probably the initial driving force for the self-assembly process.[1,2] Furthermore, hydrogen bonding also seems to play a role in the orientation of molecules within aggregates. Therefore, to obtain further insight into the structure−

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function relationships of sugar-based hydrogelators, we have constructed a small library of sugar derivatives that contain an aromatic moiety (i.e., azobenzene) linked to the saccharides via amide bridges (Scheme 1).[5] In this paper, we focus

Scheme 1. Structures of Sugar-Based Gelators
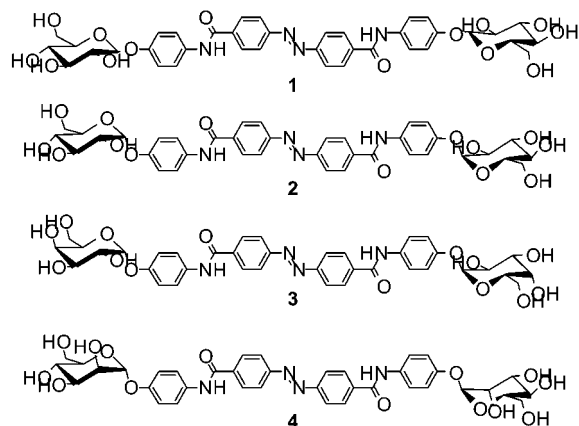
on one of the compounds of this library, the β-D-glucopyranosyl derivative **1**,[5] which has proven to be a "supergelator" for water. To the best of our knowledge, this is the first gelator able to gelate water at concentrations lower than 0.1 wt %.

To test the gelation ability of compound **1** in water, samples containing decreasing concentrations of **1** were prepared (Table 1). Gelation of **1** occurred even at concen-

Table 1. Gelation Capability and Sol−Gel Phase Transition Temperatures for Different Concentrations of **1** in H_2O (G, Transparent Gel; G_p, Partially Gelated; −, Could Not Be Determined)

concentration			
wt %	mM	**1**	T_{gel} (°C)
0.02	0.26	G_p	−
0.04	0.51	G_p	−
0.05	0.65	G	−
0.06	0.77	G	−
0.08	1.03	G	32
0.12	1.54	G	40
0.20	2.57	G	58
0.30	3.86	G	82
0.40	5.15	G	118

trations as low as 0.05 wt % (0.65 mM) and could still be partially observed at 0.02 wt %. All other hydrogelators reported so far in the literature[2] can gelate water at concentrations above 0.1 wt %. Only one amino acid based gelator has been reported to form gels at submillimolar concentrations (0.015 wt %);[2c] however, the solvent gelated by this particular compound was water containing 25 vol % DMSO. Furthermore, concentration-dependent T_{gel} measure-

ments[6] for samples of **1** in water showed that the T_{gel} value increases as the concentration of **1** increases, with a maximum for the 0.4 wt % sample for which the T_{gel} value measured (118 °C) in a sealed tube lies above the boiling point of the solvent.

To gain a better understanding of the interactions taking place between molecules in the aqueous gel of **1**, gelation studies were also carried out in DSMO/H_2O mixtures (Table 2). Although gelation occurs equally well for all mixtures

Table 2. Gelation Capability and Sol−Gel Phase Transition Temperatures for **1** (3 wt %) in DMSO/H_2O Mixtures (G, Transparent Gel; S, Solution after Cooling)

DMSO:H_2O	**1**	T_{gel} (°C)
0:100	G	184
20:80	G	167
40:60	G	153
50:50	G	115
60:40	G	73
80:20	S	
100: 0	S	

containing between 0 and 60% DMSO, the T_{gel} values decrease considerably with increasing DMSO content of the samples, giving rise to a maximum T_{gel} value of 184 °C for the 100% H_2O sample.[7] These results show that the gel of **1** is destabilized by the presence of DMSO. Therefore, aromatic $\pi-\pi$ stacking of the azobenzene moieties is most probably the principal driving force for the gelation of **1** in water. Further insight into the aggregation mode for the azobenzene moieties of **1** in the gel fibers was obtained by UV−vis spectroscopy, as well as circular dichroism (CD) measurements. The UV spectrum of a 0.08 wt % gel of **1** in water shows an absorption maximum for the azobenzene moiety at 327 nm (Figure 1).

This λ_{max} is shifted to lower wavelengths, by about 20 nm, in comparison to the same absorption peak in a DMSO solution sample of **1**.[8] According to previous studies on spectral changes arising from the aggregation behavior of

(4) (a) Kobayashi, H.; Amaike, M.; Jung, J. H.; Friggeri, A.; Shinkai, S.; Reinhoudt, D. N. *Chem. Commun.* **2001**, 1038. (b) Gronwald, O.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1933. (c) Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S. *Carbohydr. Res.* **2001**, *331*, 307. (d) Amaike, M.; Kobayashi, H.; Shinkai, S. *Chem. Lett.* **2001**, 620. (e) Amaike, M.; Kobayashi, H.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2553. (f) Amanokura, N.; Kanekiyo, Y.; Shinkai, S.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1995. (g) Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinhoudt, D. N. *Tetrahedron* **2000**, *56*, 9595.

(5) Synthesis and gelation studies of all compounds in this library will be published as a full paper elsewhere.

(6) T_{gel} was determined by placing an inverted, sealed tube in a thermocontrolled oil bath and increasing the temperature at a rate of 1 °C min^{-1}. Here, T_{gel} is defined as the temperature at which the solvent begins to flow out of the gel (± 3 °C). This temperature is lower than the temperature at which complete melting of the gel occurs. For the 0.05 and 0.06 wt % samples, inversion of the sample vials caused a small amount of water to flow out of the gels already at room temperature. This phenomenon is frequently observed for aqueous gels of low molecular weight compounds.

(7) For samples containing 40, 50, and 60% DMSO, solvents did not flow out of the gel before gel melting occurred; therefore, the reported T_{gel} values are those at which the gel completely melted.
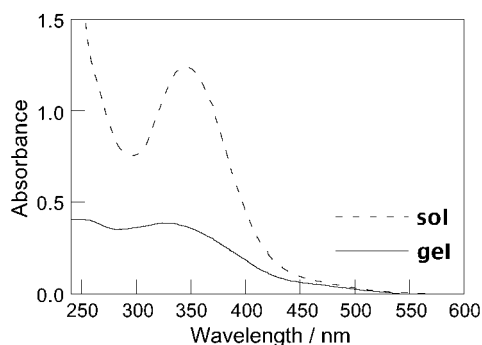
Figure 1. UV spectra of a 0.08 wt % gel of **1** in water (solid line) and of a solution sample of **1** in DMSO (broken line).

azobenzene,[9] shifts of λ_{max} to lower wavelengths point to the formation of H-type aggregates.

Such a shift of λ_{max} was also observed in DMSO−H$_2$O solution samples of **1** (0.08 wt %) upon going from high to low concentrations of DMSO (Figure 2). Therefore, as the
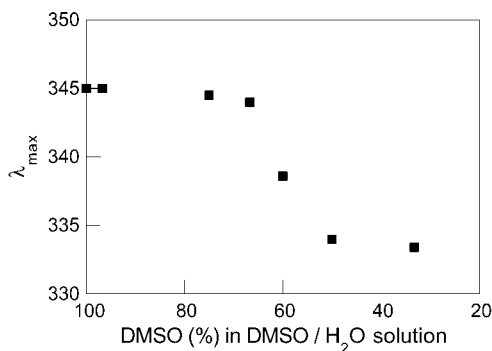
Figure 2. Shift in λ_{max} as a function of the DMSO content in DMSO−H$_2$O solutions of **1** (0.08 wt %).

solution becomes more water rich, aromatic $\pi-\pi$ stacking between the azobenzene moieties is favored and H-type aggregation takes place.

To obtain insight into the contribution of the intergelator hydrogen bonding, we measured ATR−IR spectra of the sol and gel phases (3 wt %, room temperature). The $\nu_{C=O}$ bands appeared at 1662 cm^{-1} in DMSO (sol), 1647 cm^{-1} in 80:20 v/v DMSO/D$_2$O (sol), 1638 cm^{-1} in 60:40 v/v DMSO/D$_2$O (gel), and 1641 cm^{-1} in D$_2$O (gel). These results indicate that the amido groups interact with each other using hydrogen bonding.

Transmission electron microscopy (TEM) images, as well as scanning electron microscopy (SEM) images of an

(8) The solution sample had to be prepared in DMSO due to the low concentration at which **1** becomes soluble in water.

(9) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Kunitake, T. *Nouveau J. Chim.* **1987**, *11*, 139. (c) Kunitake T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 709.

unstained xerogel[10] of **1** (0.08 wt %), revealed a network structure composed of right-handed helical bundles of fibers (Figure 3a and b). The diameter of each bundle was found to be 30−60 nm. Since the molecular length of **1** is approximately 30 Å, each bundle can be thought to consist of 10−20 individual fibers. The helicity of the bundles of fibers was investigated at the molecular level by CD spectroscopy. Gel samples of **1** (0.08 wt %) showed first a positive Cotton effect (λ_{max} 357 nm) followed by a negative Cotton effect (λ_{min} 314 nm) (Figure 4). Since the $\lambda_{\theta=0}$ value
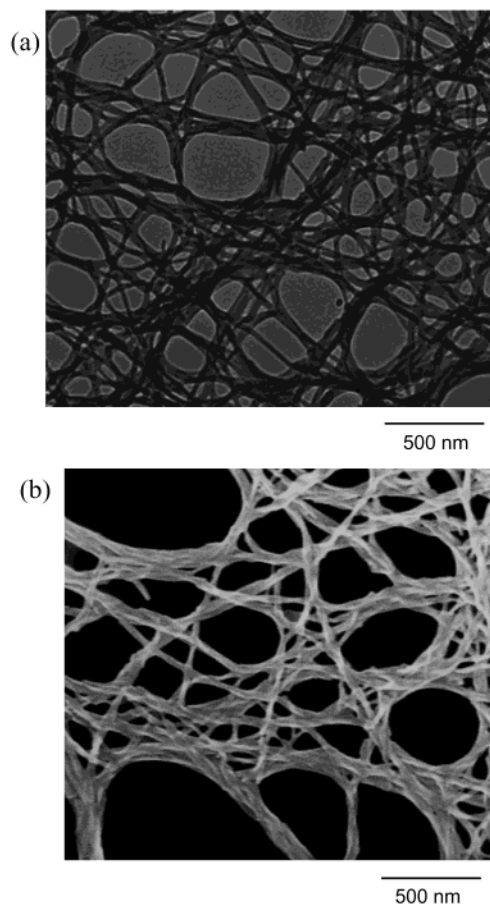
Figure 3. TEM (a) and SEM (b) images of a xerogel of **1** (0.08 wt %).

(335 nm) is comparable with the λ_{max} value (335 nm), one can attribute these bands to an exciton coupling. Thus, this behavior implies that the azobenzene moieties of the gelator molecules are stacked in a clockwise direction, i.e., with right-handed helicity. This microscopic helicity is, therefore, reflected in the macroscopic helicity observable with SEM. Moreover, this type of helicity is most probably induced by the presence of the D-glucose molecules of the gelator since low molecular weight D-glucose derivatives are known to give rise to right-handed helical structures.[11] Of the four

(10) The xerogel of **1** was obtained by freezing and pumping the gel of **1** for 12 h.
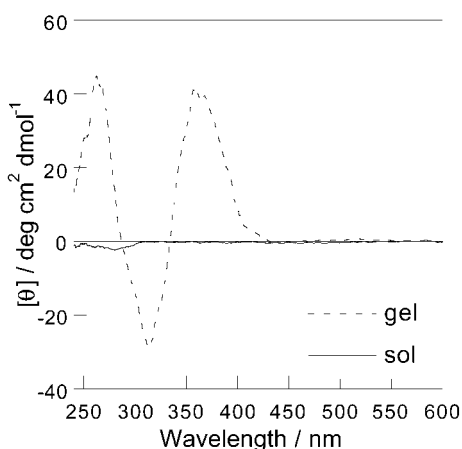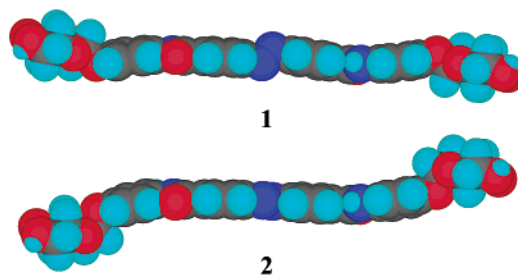
Figure 4. CD spectra of a 0.08 wt % gel of **1** in water (solid line) and of a solution sample of **1** in DMSO (broken line).

compounds shown in Scheme 1, only **1** can act as an aqueous gelator. In an attempt to find out why, the energy-minimized structures of **1** (β-isomer) and **2** (α-isomer) have been calculated and are shown in Scheme 2.[12] The structure of **1** is almost planar, which enables this gelator to enjoy both $\pi-\pi$ stacking interactions among the azobenzene groups and hydrogen bonding between the OH moieties of the saccha-

rides. On the other hand, **2** has a structure in which the two L-shaped sugar moieties are linked to the azobenzene core. Such a structure hinders the formation of cooperative $\pi-\pi$ stacking and hydrogen-bonding interactions and might explain the superiority of **1** over **2** as a gelator.

In conclusion, an accurate image of the molecular architecture of the hydrogel of **1** can be proposed, on the basis of the experimental evidence collected from T_{gel}, UV−vis, TEM, SEM, and CD measurements, and from molecular-modeling calculations. We are currently investigating a small library of sugar-based azobenzene derivatives (Scheme 1) to learn more about the determining role of the saccharide in the gelation process and further develop robust and versatile gelators from sugar derivatives.

Note Added after ASAP: This Letter was released ASAP on 3/19/02 with incorrect reference citations in the text. The print and final Web version (3/26/02) are correct.

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(12) Energy minimization of **1** was carried out by MM3 using AccuModel 1.0 (Microsimulation, L. A. Systems, Inc.) on a Macintosh computer and by MOPAC PM3 using CS Chem-office Chem 3D (CambridgeSoft Corporation) on a NEC computer. The heat of formation calculated by MOPAC PM3 for the molecular structure shown in Scheme 2 was estimated to be −2131 kJ/mol.