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An Attempt to Predict the Gelation Ability of Hydrogen-bond-based Gelators Utilizing a Glycoside Library

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Abstract—The correlation between the saccharide crystal structure and its gelating ability seems to be a useful tool for finding promising gelators. By analogy to the other types of the hydrogen-bond-based gelators the tendency to form one-dimensional hydrogen-bonded networks may be essential as a prerequisite for good gelators. The gelation abilities were tested for four configurational isomers (methyl-4,6-*O*-benzylidyne-α-D-glucopyranoside, methyl-4,6-*O*-benzylidyne-α-D-allopyranoside, methyl-4,6-*O*-benzylidyne-α-D-altropyranoside, and methyl-4,6-*O*-benzylidyne-α-D-idopyranoside) which exhibit quite different hydrogen-bonded networks in their crystal structures. Only in the case of one-dimensional hydrogen-bonded architecture the good gel systems were found.

Introduction

The development of new gelators of organic fluids has recently received much attention. They not only gelatinize various organic solvents but also create novel fibrous superstructures which can be characterized by TEM pictures of the organogels and SEM pictures of xerogels.[1–11] The gelators can be classified into two categories according to the difference in the driving force for the molecular aggregation, viz. hydrogen-bond-based gelators and non-hydrogen-bond-based gelators. Typical examples of the former group are aliphatic amide derivatives,[1–4] and of the latter group are cholesterol derivatives.[6–9] For both systems, the formation of crosslinked network structures is indispensable to gelation because they efficiently suppress the solvent fluidity as crosslinked polymeric gelators do.[1–11] It is now possible, therefore, to explain *how the organogel is formed*. In contrast, it is still very controversial to rationalize *why the organogel is formed*. One potential approach to this controversy from a macroscopic viewpoint would be rheological methods as devoted by Terech and a few others.[5,6] It seems to us, however, another potential approach from a microscopic, molecular-level viewpoint has still escaped attention. Recently, it was shown that the organogel fibers are not so 'wet' with solvent molecules and possess more or less the crystal-like characters.[5,7,9,12] This implies that the mechanism of the organogel fiber formation may be explicable in relation to the crystal structure formation of gelators. In nonhydrogen-bond-based gelators, the molecular packing displayed none of the characteristics expected of the gelator fibers.[5a,f] In hydrogen-bond-based gelators, in contrast, the significant similarity was found between the organogel fiber structure and the crystal structure[1b] although the organogel fiber structure is somewhat more disordered than the crystal structure.[9] The difference suggests an advantage of hydrogen-bond-based gelators in making an approach for the microscopic, molecular-level viewpoint.

Results and Discussion

Among many different types of hydrogen-bond-based gelators, saccharides seem to be the old but still new and not yet fully explored gelators and meet the present purpose. Several previous reports have shown that saccharides have high potentials in gel formation, however some of them do not form gels at all.[13–15] The aim of this work was to find the method which could help us to predict the gelating ability and thus minimize the synthetic effort. We excepted that this approach could explain the basic requirements for a saccharide to be a good gelator. By analogy to other types saccharides form hydrogen-bond-based chains that are building blocks of the fibril-like gelator structure. We thus expected that the way in which saccharide molecules are arranged in the crystalline state should reflect its gelation ability. This assumption may be supported by the fact that FT-IR spectra of saccharide gels show the presence of intermolecular hydrogen bonds while no such interactions were

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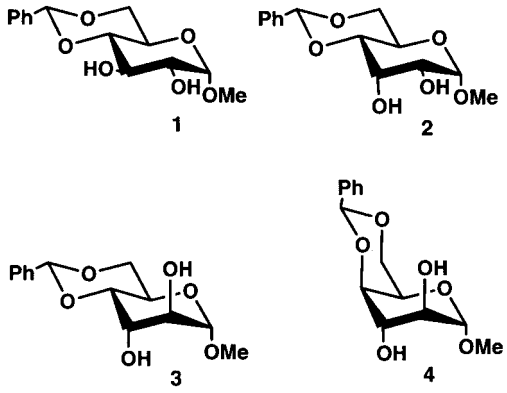

Figure 1. Investigated sugars.

detected in dilute solutions.[14,15] To find potential correlation between the gelation ability and the crystal structure, four different saccharides representing different hydrogen-bonded networks were chosen: they are methyl-4,6-*O*-benzylidyne-α-D-glucopyranoside (**1**), methy1-4,6-*O*-benzylidyne-α-D-allopyranoside (**2**), methyl-4,6-*O*-benzylidyne-α-D-altropyranoside (**3**), and methyl-4,6-*O*-benzylidyne-α-D-idopyranoside (**4**) (Fig. 1). These four compounds are common in having (i) unmodified 2-OH and 3-OH, (ii) 1-OH protected by a methyl group, and (iii) 4-OH and 6-OH protected by a benzylidene group, whereas their crystal structures are different solely due to configurational isomerism. The gelation ability of these four saccharides is summarized in Table 1. It is seen from Table 1 that **1** is classified into a good gelator as shown by six G* and G marks (see a footnote for abbreviations). The solubility of **2** is comparable with that of **1**, but several G* and G marks in **1** are changed into P marks in **2**. Compound **3** is very insoluble as shown by many I* and P* marks. On the other hand, **4** is relatively soluble in many organic solvents. Neither **2**, **3** nor **4** results in good organogels. Why are the gelation properties so different among configurational isomers?

Table 1. Organic solvents tested for gelation by **1**–**4** (G=gel 3.0% (wt/vol), P=precipitation, Ps=self-supporting precipitation, Pps=partial-self-supporting precipitation, S=solution, I=insoluble, *=the same result was obtained at 1.0% (wt/vol))

Solvent	1	2	3	4
n-Hexane	Ps*	P*	I*	Ps
n-Heptane	Ps*	P*	I*	P*
n-Octane	Ps*	P	P*	P
Cyclohexane	Ps*	P	P*	P*
Methylcyclohexane	Ps*	P	Pps*	P
Benzene	G	Pps	Pps	S
Toluene	G*	Pps	Pps	S
p-Xylene	G*	Pps	Pps	S
Nitrobenzene	S	S	S	S
Carbon tetrachloride	G*	P	P*	P
Carbon disulfide	P*	P*	P*	Pps
Diethyl ether	S	P	P*	S
Diphenyl ether	G	Pps	Pps	S
Ethyl formate	S	S	S	S
Methyl acetate	S	S	S	S
n-Octanol	S	S	S	S
Triethylamine	S	S	S	P
Triethylsilane	Ps*	P	S	P*
Tetraethoxysilane	G*	P	Pps*	P
Water	Ps	S	S	P
1,2-Dichloroethane	S	S	S	S
Dichloromethane	S	S	S	S
Chloroform	S	S	S	S
Ethyl acetate	S	S	P	S
Ethyl malonate	S	S	S	S
Acetone	S	S	S	S
Methyl ethyl ketone	S	S	S	S
Acetonitrile	S	S	S	S
Ethanol	S	S	S	S
n-Propanol	P	S	S	S
n-Butanol	P	S	S	S
Hexanoic acid	S	S	S	S
Acetic anhydride	S	S	S	S
Glycerol	S	S	S	S

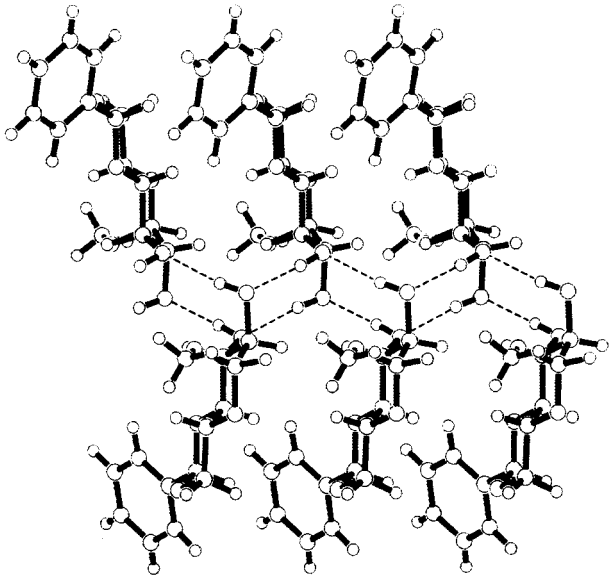

Figure 2. Chain fragment in **1**.

The crystal structures of **2**,[16] **3**,[17] and **4**[18] have been determined and available from the Cambridge Structural Database. To obtain an insight into the packing mode of **1** we grew up the single crystal from ethyl acetate (the same crystal structure was found for crystals grown from gelating solvents, but their quality was worse). The crystal structure was successfully solved as shown in Fig. 2. As shown by Hanabusa et al.[1] for amide-based gelators and by Feringa et al.[19] for urea-based gelators, good gelators tend to form one-dimensional hydrogen-bonding array. In the solid state **1** forms one-dimensional zigzag chains in which molecules are connected by two hydrogen bonds using 2-OH and 3-OH. These characteristics of **1** seem to fully satisfy the structural prerequisites as a gelator.

Compound **2** also exhibit a one-dimensional chain structure (Fig. 3a).[16] In this case, however, the molecular packing is supported by only one intermolecular hydrogen-bond and the second one is used for the intramolecular 3-OH···1-OMe interaction. Hence, **2** basically satisfies the primary prerequisite to be one-dimensional. In the gel phase where the intermolecular hydrogen-bonding interaction must compete with the solvation, however, the fibrous structure cannot be so stabilized as that of **1**. The unstability gives rise to the disordered structure including free OH groups,

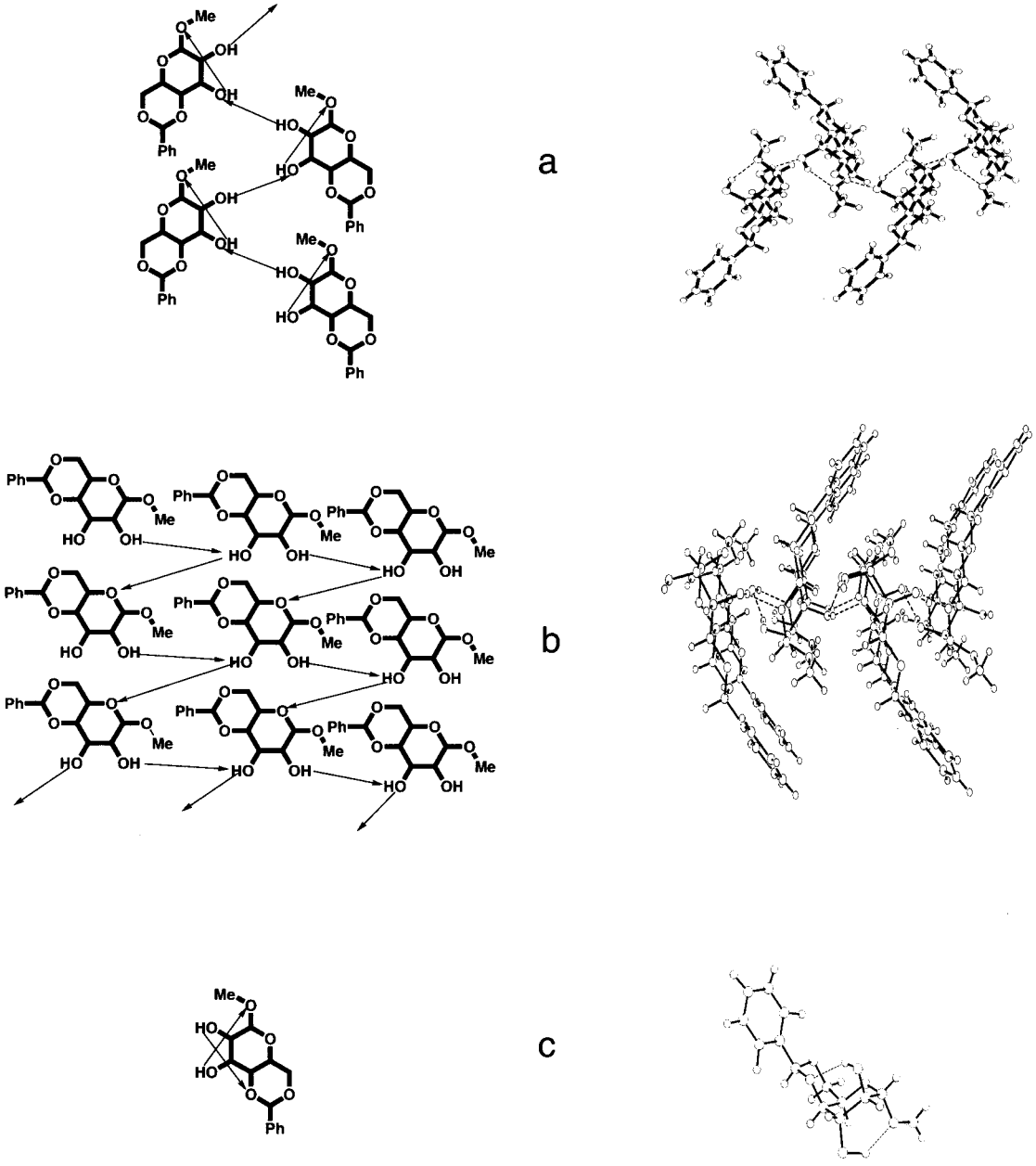

Figure 3. Schematic representation and structure fragments of hydrogen-bond network in **2** (a), **3** (b) and **4** (c). Arrows describe the hydrogen bonds (from donor to acceptor).

the hydrogen-bonds of which eventually result in the three-dimensional, insoluble aggregates. This situation is reflected by many P and P* marks for which **1** can give G and G* marks.

The crystal structure of compound **3** features saccharide molecules connected by two OH groups and 5-ethereal oxygen into two-dimensional layers (Fig. 3b).[17] As the result, **3**, which cannot construct the one-dimensional hydrogen-bonding array, does not act as a gelator and shows the solubility lower than the compounds constructing the one-dimentional hydrogen-bonding array. In compound **4**, on the other hand, two OH groups are both used to form the intramolecular hydrogen-bonds and no significant intermolecular hydrogen-bond is found in the crystal structure (Fig. 3c).[18] This structure may be called zero-dimensional hydrogen-bonding array. As expected, compound **4** is very soluble in many organic solvents. The crystal structure which features the three-dimensional hydrogen-bonding array is not found so far (for this class of compounds), but it is undoubted that such saccharides do not act as good gelators. This may be supported by the fact that three-dimensional hydrogen-bonded network is characteristic of saccharides possessing three or four free OH groups. Many such examples exist in Cambridge Structure Database but none of them have been reported as a good gelator (e.g. α-D-glucose,[20] α-D-galactose,[21] β-D-galactose,[22] β-D-allose,[23] etc.). On the other hand, saccharides possessing only one free OH group tend to exhibit one-dimensional hydrogen-bonded network,[24–28] but in this case only one hydrogen-bond can be used for an intermolecular connection, which makes the chain relatively weak and flexible. This situation is similar to the present system found in crystal structure of

compound **2**. Thus, saccharides having two free OH groups seem to be ideal candidates to be a good gelator. Either three-, two- or zero-dimensional hydrogen-bonded networks are probably very rare in this class of compounds.[29] In the preceding references, no three-dimensional network is found and except compound **3** only one layered structure of methyl-3,4-*O*-(1-(*R*)-(methoxycarbonyl)ethylidene)-β-D-galactopyranoside is present.[30] In this case we may expect it to be a poor gelator. However, it must be underlined that the problem is much more complicated—the gel fibril and crystal structures do not have to be identical. In other words, the gel fibril is not just a very long and thin crystal. On the other hand, to form such elongated fibrils the growth in one direction should be much faster than in the others. It means that the responsible driving forces must be different. In the case of saccharides this difference may be realized by presence of two main interactions: hydrogen bonding and van der Waals forces. While the hydrogen bonds are responsible for growth along the fibril axes, the van der Waals interactions makes the fibril thicker. It can be controlled by the solvent which may prevent or slow down the growth perpendicular to fibril axes. From this point of view the tendency of gelator molecules to self-assembling and form long, hydrogen-bond-based chains seems to be very important. Unfortunately, especially in the case of saccharides which have quite compact molecules, the presence of such chains, instead of layers, isolated dimmers cannot be easy predicted. This is why the analysis of their crystal structures seems to be very helpful. The presence of one-dimensional hydrogen-bonded network may suggest that the saccharide molecules tends to assemble in chains, and be useful for finding 'promising' gelators, however the problem is quite complex and gel formation cannot be explained univocally by determining only on decisive factor. In other words, this requirement is rather indispensable than sufficient. This approach, is also limited to the solvents which cannot make strong hydrogen-bonds. In water or alcohols the gelating mechanism may be completely different. Fortunately, in general, saccharides do not tend to make gels with such solvents.[31] One reason is, of course, that this type of solvent may act as chain growth inhibitor. However, another explanation is also possible: solvent molecules (especially water) can rebuild a hydrogen-bonded network and in most cases increase its dimensionality (up to two- or three-dimensional). Now, when the growth process can be driven by hydrogen-bonding in all directions precipitation is more probable.

In conclusion, the present paper demonstrated the potential correlation between the gelation ability and the crystal structure. Of course, we fully understand that there are some exceptions from this methodoloy, but this is very useful to efficiently choose appropriate saccharides and skillfully design good gelators. This kind of microscopic, approach seems to be important especially in the case of the large saccharide library where the finding of a good gelator, very often, is the matter of chance. Furthermore, there is a future possibility to discover new super-gelators from the saccharide library which satisfy the prerequisites described in this paper. In fact, we have found that methyl-4, 6-*O*-*p*-nitrobenzylidene-α-D-galactopyranoside acts as one of the strongest gelators discovered so far.[32]

Experimental

Crystal data for **1**: $C_{14}H_{18}O_6$, M_r=282.29, orthorhombic, space group $P2_12_12_1$(no.19), a=8.950(1), b=32.083(3), c=4.8449(4) Å, V=1391.3(2) Å^3, $F(000)$=600, ρ_{calcd}=1.348 g cm^{-1}, Z=4, μ(CuKα)=8.92 cm^{-1}, crystal dimension 0.1×0.1×0.1 mm, 1515 reflections collected, $2\theta_{max}$=136.4°, 1491 independent reflections, $R1$=0.039 for 1134 reflections with $I>2\sigma(I)$, wR=0.055 (for all data), S=0.74. Data collected at room temperature, Rigaku RAXIS-RAPID Imagine Plate diffractometer, structural solution by direct methods, full-matrix least-squares refinement on F^2. Hydrogen atoms refined as isotropic. Calculations were performed using teXsan package. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no CCDC-141743. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). The gelation test was carried as follows: the gelator (3.0 mg) was mixed with carefully dried solvent (0.1 mL) in a sealed tube and the mixture was heated until the solid dissolved (frequently above solvent bp). The solution was cooled to room temperature and left for 1 h. In the case of G and I the sample was diluted and tested again at 1.0 wt%. Compounds **1**, **2**, **3** and **4** were synthesized according to the methods described in the literatures.[14b,33–35]

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