Chirality-dependent Gel Formation from Sugars and Boronic-acid-appended Chiral Amphiphiles

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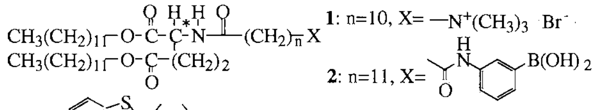
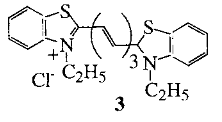
Aqueous solutions containing a boronic-acid-appended amphiphile with a L-glutamate segment were gelatinized in the presence of certain saccharides. Examination of the gelation temperature, DSC, and the absorption spectra of a cyanine dye revealed that this is a novel system having two phase-transitions, *viz.*, the sol-gel phase transition and the gel-liquid crystal phase transition.

We have recently been interested in molecular design of a new sugar recognition system useful in aqueous media.[1,2] We have already demonstrated the validity of the boronic acid as a saccharide receptor functional group, because the reaction with saccharides to form a covalent boronate linkage can take place rapidly and reversibly even in aqueous media.[1-5] This is a big advantage of the boronic acid function over the hydrogen-bonding function which is nearly useless in aqueous media. It has thus become possible to utilize a variety of saccharide molecules, abundant natural resources as a chiral auxiliary for boronic-acid-appended amphiphiles. Fuhrhop *et al.*[6] demonstrated that protoporphyrin IX covalently-linking two glycosamines as a chiral auxiliary can form ordered aggregates in aqueous media. We demonstrated that the similar but more diversiform, chiral aggregates can be created by simply mixing saccharides with a boronic-acid-appended porphyrin[7] or with a boronic-acid-appended azobenzene-containing amphiphile.[8] These novel findings suggest that the boronic acid-saccharide interaction may be useful as a novel strategy to change the morphology of aggregates formed in aqueous media. If this idea works as expected, it would serve as a potential model system for the saccharide control of the cell morphology. Meanwhile, Kunitake *et al.*[9] already showed that amphiphile **1** prepared from L-glutamic acid forms stringy aggregates in aqueous media and some of them possess a helical higher-order structure. The results tempted us to synthesize a new amphiphile **2** bearing a boronic acid group. Our original idea was to control the morphology of the aggregates by added saccharides. We unexpectedly found, however, that in the presence of saccharides **2** tends to gelatinize the aqueous solution and the gelation is dependent upon the saccharide chirality.





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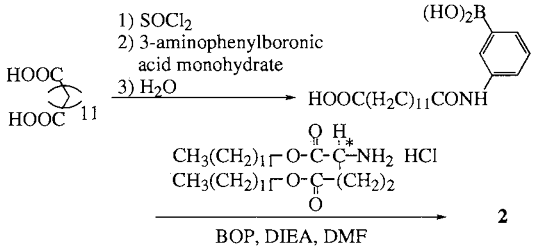
Amphiphile **2** (mp 52.4-54.6 ℃) was synthesized according to Scheme 1 and identified by IR and ^{1}H NMR spectral evidence and elemental analysis.



Scheme 1.

Since **2** is not so soluble in water, the measurements were carried out mainly in a water/methanol (70:30 v/v) mixture. A methanol solution (3 ml) containing **2** and an aqueous solution (7 ml: pH 10.5 with 50 mmol dm^{-3} carbonate) containing saccharide were mixed. The solutions were sonicated for 30 min and then cooled to 5 ℃. In the absence of saccharides **2** could not be dispersed into this medium. In contrast, most solutions were gelatinized in the presence of saccharides (Table 1). At [**2**]= 2.50 mmol dm^{-3}, for example, the **2** + L-glucose system and the **2** + D-fucose system provided a gel whereas the **2** + D-glucose system and the **2** + L-fucose system provided a viscous solution. At [**2**] = 5.0 mmol dm^{-3}, the gels were formed at 25 ℃ both from D- and L-glucose at 0.50 mol dm^{-3} but the gel was formed only from L-glucose at 0.20 mol dm^{-3}. In fructose L-isomer gave the more stable gel with **2** than D- isomer (Table 1). These chiral discrimination phenomena are due to the L-glutamate chiral segment in **2**. The foregoing results indicate that L-glucose, D-fucose, and L-fructose bound to the aggregate surface facilitate the gelation of **2** more efficiently than D-glucose, L-fucose, and D-fructose, respectively.

At [**2**] = 5.00 mmol dm^{-3} and [saccharide] = 1.00 mol dm^{-3}, the sol-gel phase-transition (T_{gel}) was observed at 43-54 ℃ for L-glucose and 45-53 ℃ for D- fucose. In DSC a broad peak appeared at 58-64 ℃ (ΔH = 39 kJ mol^{-1}) for L-glucose and 58-64 ℃ (ΔH = 32 kJ mol^{-1}) for D-fucose. There peaks were observable very reproducibly. These endothermic peaks can be assigned to the gel-liquid crystal phase-transition temperature (T_c) because the T_c appeared above the T_{gel}. The T_c was also observable for the viscous solutions of the **2** + D-glucose system (59-66 ℃; ΔH = 38 kJ mol^{-1}) and the **2** + L-fucose system (58-64 ℃; ΔH = 16 kJ mol^{-1}). One can conclude, therefore, that the present gels are novel systems consisting of two different phase-transitions.[10]

Here, we considered that these two phase-transitions might be detected separately by absorption spectroscopy of dye molecules. We thus chose a cationic cyanine dye **3** which is known to be bound to the boronate anion center.[1d] Both L- and D-fructose gave two absorption maxima at 663 nm (aggregate) and 571 nm (monomer)[1d] with **2**. From the plots of the absorbance versus temperature (Figure 1) one can raise two very interesting facts: (i) there are two phase-transition temperatures which can be attributed to T_{gel} and T_c, respectively and (ii) below T_c, the plot for L-fructose appears above that for D-fructose. The results indicate that the chiral discrimination is partly executed in the gel phase between **2** and fructose.

To obtain a visual insight into the aggregate structure, we observed the aggregation mode of **2** in the presence of saccharides by TEM. The amphiphiles were first sonicated in an aqueous solution with saccharides and then shadowed with phosphotungstic acid.[11] The results are summarized in Table 1. The morphologies under the TEM observation can be classified into five categories: (1) well-developed helical strings, (2) helical strings, (3) strings without a helical structure, (4) trace strings without a helical strings, and (5) no structure. For example, category (1) was observed for D-fructose, D-galactose (monosaccharides) and D-cellobiose and D-maltose (disaccharides). One can consider, therefore, that these saccharides can facilitate the formation of a helical structure because their configurations are compatible with the structure of the boronic-acid-appended surface created by the L-glutamate skeleton. The typical TEM picture is shown in Figure 1. It is seen from Figure 2 that these strings have a right-handed helical structure. On the other hand, categories (4) and (5) were observed for D-mannose, D-fucose, and D-xylose. Comparison of D- and L-isomers of glucose and fucose suggests, however, that there is not a close relationship between the gelation ability and the aggregate structure.

Table 1. Solution state at 5 ℃ and TEM observation of the dried samples

Saccharide	Solution at 5 ℃[a]	TEM
None	Ppt	-
D-Glucose	Gel (Viscous solution[b])	String without helix
L-Glucose	Gel [b]	String without helix
D-Fructose	Gel (unstable)[b]	Well-developed helical string
L-Fructose	Gel [b]	-
D-Aralinose	Gel	-
L-Aralinose	Gel	String without helix
D-Mannose	Gel [b]	No structure
L-Mannose	Gel [b]	-
D-Fucose	Gel [b]	String (trace) without helix
L-Fucose	Gel (Viscous solution[b])	Helical string
D-Galactose	Gel	Well-developed helical string
D-Xylose	Gel	String (trace) without helix
L-Xylose	-	String without helix
L-Ribose	Gel	Helical string
D-Ribose	-	Helical string (trace)
L-Threitol	-	Helical string
D-Cellobiose	-	Well-developed helical string
D-Maltose	-	Well-developed helical string

[a] [2] = 5.00 mmol dm^{-3}, [saccharide] = 1.00 mol dm^{-3}, water (pH 10.5 with 50 mmol dm^{-3} carbonate): methanol = 70:30 *v/v*.

[b] [2] = 2.50 mmol dm^{-3}, [saccharide] = 0.50 mol dm^{-3}.

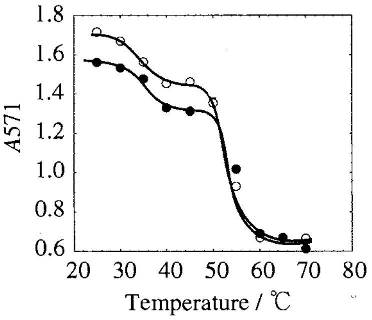


Figure 1. Plots of absorbances of **2** (2.50 mmol dm^{-3}) at 571 nm (aggregate) in the presence of D- (●), or L- (○) fructose (1.00 mol dm^{-3}).

Figure 2. TEM picture of **2** in the presence of L-threitol which has a right-handed helical string.

In conclusion, the present study demonstrated that the aggregation morphologies of **2** can be controlled by a boronic acid-saccharide interaction which occurs at the aggregate surface. We consider that this attempt is interesting in relation to the imitation of certain cell membranes which have saccharide-recognition sites on the cell surface and change their morphology in response to added saccharide structures. More in general, we believe that this concept will become a novel method for the control of aggregate morphologies and their related functions by physiologically-nontoxic saccharides.

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11 For the detail of the TEM sample preparation see Ref. 8.