

## Selective Molecular Recognition of Disaccharides by a Biphenyldiboronic Acid at the Air -Water Interface

Claus Dusemund, Masafumi Mikami, and Seiji Shinkai\*  
 Shinkai Chemirecognics Project, Research and Development Corporation of Japan,  
 Kurume Research Center Building, Aikawa 2432-3, Kurume, Fukuoka 830

(Received November 28, 1994)

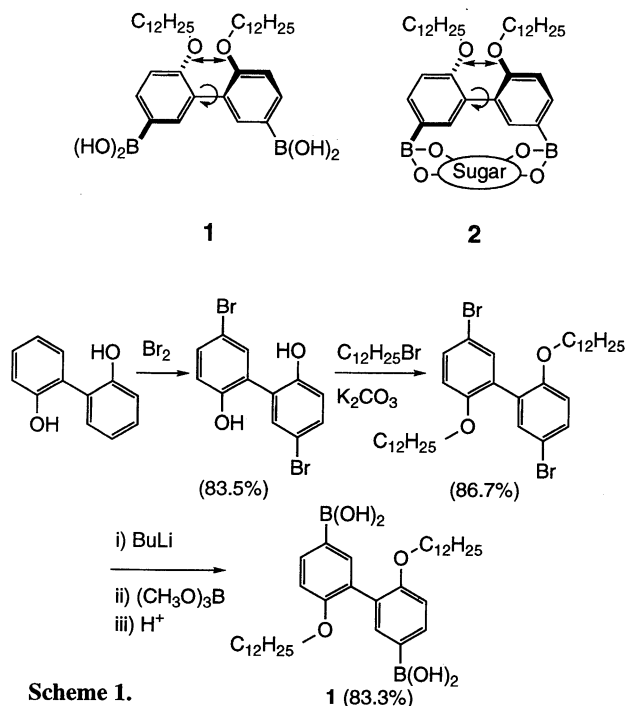
A biphenyldiboronic acid derivative can be used for molecular recognition of disaccharides at the air-water interface. Disaccharides are detected selectively because of the fixed distance between the boronic acid moieties in the molecule and the organized structure of the monolayer.

As monolayers can be simple models of cell membranes, molecular recognition at the air-water interface could provide some insight into biological cell functions. Saccharides are one of the most important species in cell functions. Previously, the hydrogen bonding interaction has been utilized in recognition of saccharides by resorcinol-dodecanal cyclotetramer monolayer at the air-water interface.<sup>1</sup> On the other hand, the covalent interaction of boronic acid with saccharides is found to be useful in saccharide recognition in homogeneous aqueous systems.<sup>2-5</sup> Amphiphilic monoboronic acids have been utilized in recognition of saccharides at the air-water interface.<sup>6</sup> Cholesteryl boronic acid has been used in chiral recognition of monosaccharides in the air-water interface<sup>7</sup> and also in liquid crystal systems.<sup>8</sup> It has been reported that cooperative binding of diboronic acid is dependent on the distance between two boronic acid units.<sup>3</sup> The selectivities towards different mono- and disaccharides have been achieved by changing the distance between two boronic acid moieties. The boronic acid moiety has been modified recently by Shinkai *et al.*<sup>5,9</sup> to create fluorescence saccharide sensors not only by monoboronic acid but also by cooperative binding of diboronic acid.

In this paper, we report molecular recognition of disaccharides by 2,2'-didodecyloxybiphenyl-5,5'-diboronic acid **1** at the air-water interface. Lactose and cellobiose have an strong effect on the molecular area. Monosaccharides such as fructose and glucose, which are normally relatively strongly bound to phenylboronic acids, have only small effects on the surface area; therefore **1** has the ability to selectively recognize disaccharides.

Compound **1** was synthesized according to Scheme 1.<sup>10</sup> Monolayers of **1** were prepared by spreading a benzene-THF (3:1, v/v) solution on an aqueous subphase containing KHCO<sub>3</sub> (10 mmol dm<sup>-3</sup>, pH 8.3) and disaccharide (Fluka for microbiology and TCI) with different concentrations. The film balance (San-esu Keisoku Co., model FSD-50) was on an air-suspended table in a clean-air zone. Experiments were carried out at 278 K and the waiting time after spreading before compression was 15 min. The fluorescence microscopic measurements were carried out under similar conditions by adding 0.5 mol% DPPE Rhodamine B<sup>6</sup> to the boronic acid solution. The solution of **1** (benzene/THF) was stored in a refrigerator and all experiments with the same stock solution were performed within a few days, because **1** was not so stable in the solution.

The key for selective binding is the choice of the optimal pH, which is 8.3. Efficient complexation of **1** with saccharides requires the boron atom to be sp<sup>3</sup>-hybridized anionic species (Ar-

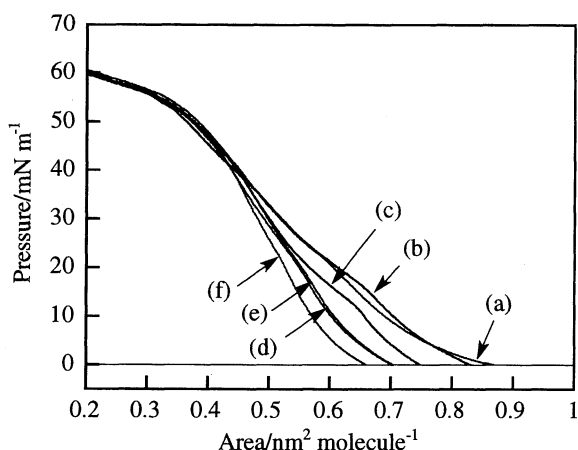


Scheme 1.

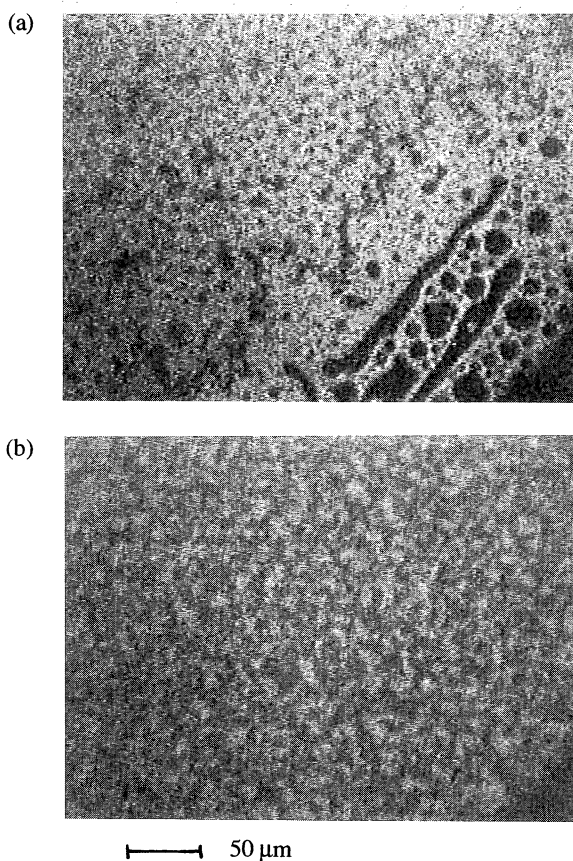
B(OH)<sub>3</sub><sup>-</sup>), which is achieved at high pH region, as also increasing the hydrophilicity. However, the monolayer of **1** becomes very rigid at higher pH region (more than pH 9.3), so that reproducibility is poor. The use of low temperature (278 K) has the advantage that the slope of the  $\pi$ -A isotherms is much more steep than at room temperature.

Fluorescence microscopic measurements (Figure 2) showed that the diboronic acid monolayer with lactose in the subphase was much more homogeneous than the uncomplexed one. The solid islands nearly disappeared after 10 min waiting (reaction) time after spreading. Therefore, the surface was stabilized by complexation with the saccharides. The uncomplexed diboronic acid formed irregular shaped islands as well as round ones. This was consistent with the phenomena that the reproducibility with sucrose solution and saccharide free solution was not so good.

We previously found that in amphiphilic monoboronic acids the expansion of the monolayer is well correlated with binding ability.<sup>6</sup> In this study, the order of take-off points is: lactose > cellobiose >> maltose, fructose, melibiose > sucrose (Figure 1). Lactose and cellobiose increase the molecular area whereas other saccharides decrease it. The difference is accounted for by the stoichiometry: Lactose and cellobiose which tend to form a cyclic 1:1 complex with **1**<sup>3</sup> increase the dihedral angle of the biphenyl moiety and the molecular area as well. On the contrary, other saccharides which tend to form a noncyclic 1:2 **1**/saccharide complex<sup>3</sup> decrease the dihedral angle and the molecular area as



**Figure 1.** Surface pressure-area ( $\pi$ -A) isotherms of the monolayer **1**. The saccharide concentration in the subphase (pH 8.3 with  $10 \text{ mmol dm}^{-3} \text{ KHCO}_3$ ) is  $20 \text{ mmol dm}^{-3}$ . The  $\pi$ -A curves were obtained at 298 K and a compression rate  $0.400 \text{ mm s}^{-1}$  on a  $350.8 \times 100 \text{ mm}$  trough with a computer-controlled film balance (San-esu Keisoku Co., model FSD-50). (a) lactose, (b) cellobiose, (c) none, (d) maltose, (e) melibiose, (f) sucrose.



**Figure 2.** Optical microscopic morphologies of **1** (containing 0.5 mol% of DPPE Rhodamine B) at 0 surface pressure: the subphase is (a)  $\text{KHCO}_3$  solution ( $10 \text{ mmol dm}^{-3}$ ) 15 min after spreading, (b)  $20 \text{ mmol dm}^{-3}$  lactose in  $\text{KHCO}_3$  solution ( $10 \text{ mmol dm}^{-3}$ ) 15 min after spreading.

well.

This order of take-off points is different from association constants found by CD measurements with biphenyl-3,3'-diboronic acid in homogeneous solution: the order of association constants was lactose > maltose > cellobiose > sucrose.<sup>3</sup> The difference is probably caused by the steric crowding of the 2,2'-positions which makes the dihedral angle bigger: that is, the distance between the two boronic acids in **1** is longer than that in biphenyl-3,3'-diboronic acid. Hence, lactose and cellobiose bearing a  $\beta$ -glucopyranoside linkage are more favored than maltose bearing a different  $\alpha$ -glucopyranoside linkage. This causes a change in the binding ability with disaccharides as the hydroxy-groups have different positions. Furthermore, a monolayer is an organized phase, different from homogeneous solutions.

In conclusion, it has been shown that diboronic acid **1** is useful in selective recognition of disaccharides at the air-water interface.

We thank Dr. Katsuhiko Ariga (Supermolecular Project, JRDC) for helpful discussion.

#### References and Notes

- 1 K. Kurihara, K. Ohto, Y. Tanaka, Y. Aoyama, and T. Kunitake, *Thin Solid Films*, **179**, 21 (1989); K. Kurihara, K. Ohto, Y. Tanaka, Y. Aoyama, and T. Kunitake, *J. Am. Chem. Soc.*, **113**, 444 (1991).
- 2 A. W. Czarnik, *Acc. Chem. Res.*, **27**, 302 (1994), and references cited therein.
- 3 K. Kondo, Y. Shiomi, M. Saisho, T. Harada, and S. Shinkai, *Tetrahedron*, **48**, 8239 (1992).
- 4 Y. Shiomi, K. Kondo, M. Saisho, T. Harada, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2111.
- 5 T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1994**, 477; K. R. A. S. Sandanayake, K. Nakashima, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1994**, 1621.
- 6 S. Shinkai, K. Tsukagoshi, Y. Ishikawa, and T. Kunitake, *J. Chem. Soc., Chem. Commun.*, **1991**, 1039.
- 7 R. Ludwig, T. Harada, T. D. James, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 697.
- 8 T. D. James, T. Harada, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1993**, 857.
- 9 T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, in press.
- 10 mp  $184\text{--}190^\circ\text{C}$  (dec.); IR (KBr,  $\text{cm}^{-1}$ ): 3200 (OH), 1352 (BO);  $^1\text{H-NMR}$  ( $\delta$ , ppm in  $\text{CDCl}_3\text{:CD}_3\text{OD} = 9\text{:}1$ , TMS): 7.63-7.50 (m, 4H, Ar-H), 6.83 (d, 2H,  $J=8.3 \text{ Hz}$ , Ar-H), 3.83 (t, 4H,  $J=6.6 \text{ Hz}$ , O- $\text{CH}_2$ ), 1.53-1.49 (m, 4H, O $\text{CH}_2$ - $\text{CH}_2$ ), 1.25-1.14 (m, 36H,  $\text{CH}_2$ ), 0.80 (t, 6H,  $J=6.7 \text{ Hz}$ ,  $\text{CH}_3$ );  $^{11}\text{B-NMR}$  ( $\delta$ , ppm in  $\text{CH}_3\text{OH}$ ,  $\text{NaBF}_4$ ): 19.63.