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Yutaka Shiomi; Kaoru Kondo; Miwako Saisho; Takaaki Harada; Kazuhiko Tsukagoshi[a]; Seiji Shinkai[b]
[a] Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka, Japan [b] Chemirecognics Project, ERATO, Research Development Corporation of Japan, Kurume, Fukuoka, Japan

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Specific complexation of saccharides with dimeric phenylboronic acid that can be detected by circular dichroism

YUTAKA SHIOMI, KAORU KONDO, MIWAKO SAISHO, TAKAAKI HARADA, KAZUHIKO TSUKAGOSHI,** and SEIJI SHINKAI*

**Chemirecognics Project, ERATO, Research Development Corporation of Japan, Aikawa 2432-3, Kurume, Fukuoka 830, Japan*
***Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan*

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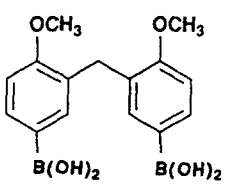
For the development of new receptor molecules that can recognize sugar molecules, we synthesized 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid (1) and diphenyl-3,3′-diboronic acid (2). It was shown that in the presence of 1, some mono- and disaccharides result in a CD band at 275 nm. It was also shown that 2 forms 1:1 complexes with several disaccharides and gives the characteristic exciton coupling in CD spectroscopy owing to immobilization of the two phenyl rings. The results indicate that the CD spectroscopic method using 1 or 2 as receptor molecules serves as a new sensory system for sugar molecules, and the absolute configuration of disaccharides was successfully predicted from the sign of the exciton coupling of the CD spectrum by using 2.

INTRODUCTION

The molecular design of receptor molecules that can precisely recognize and specifically bind guest molecules has been the focus of much recent attention.[1,2] In the papers reported so far hydrogen-bonding interactions play a central role.[3–11] It is not disputed that the hydrogen-bond has merit in precise molecular recognition: for example, the multi-point interaction between hosts and guests is possible and the spatial position of guests is controllable by the direction of the lone-pair orbitals serving as a hydrogen-bond acceptor. However, it has several demerits as well: for example, it is practically usable only in aprotic solvents and almost impotent in an aqueous system. We considered that more precise molecular recognition may be achieved through the formation of covalent bonds. Since it is scarcely affected by the presence of protic solvent molecules, it is particularly useful in molecular recognition in an aqueous system. Previously, Wulff *et al.*[12–14] demonstrated that certain saccharides are precisely recognized by two benzeneboronic acids immobilized in insoluble polymer matrices. We thus chose the recognition of saccharides in water as a research target. We recently synthesized 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid (**1**) and diphenyl-3,3′-diboronic acid (**2**). One can expect that these compounds will become CD (circular dichroism)-active only when they form 'specific' complexes with saccharide molecules. Moreover, the molecular design of **2** is based on the following new viewpoints: i) the distance between the two boronic acids (ca. 7.4 Å from the CPK model)[15] is comparable with or a little shorter than that between 1,2-diol and 4′-OH · 5′-CH_2OH (ca. 4.2–8.7 Å) in disaccharides and ii) the dihedral angle between the two benzene rings changes when the two boronic acids form a sugar complex. It is expected from i) that **2** would show selectivity toward disaccharides rather than toward monosaccharides. On the other hand, ii) suggests the possibility that the change in the dihedral angle, which is induced by complexation, would be sensitively 'read-out' with circular dichroism (CD) spectroscopy. 4-Methoxyphenylboronic acid (**3**) and diphenyl-3-boronic acid (**4**) were used as reference compounds for **1** and **2**, respectively.



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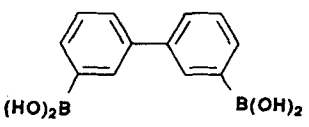

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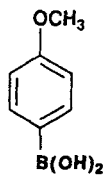

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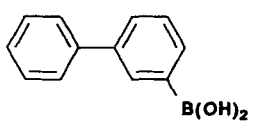

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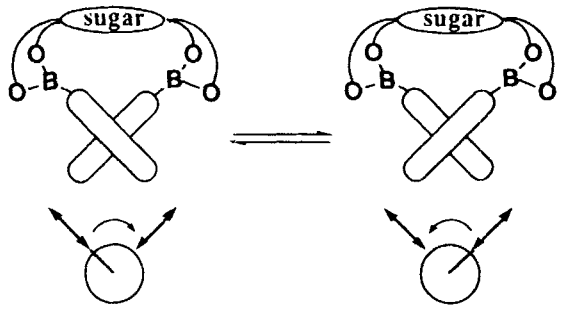
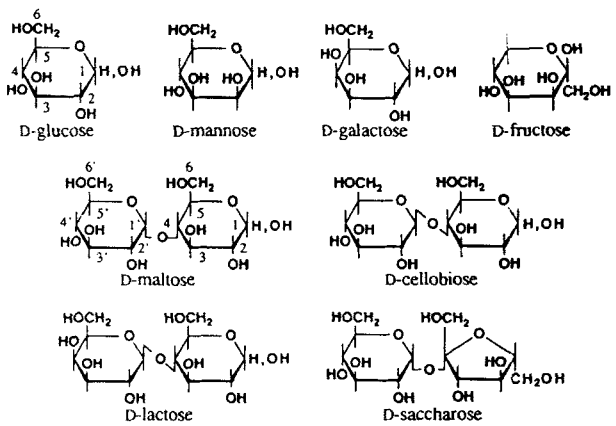
*To whom correspondence should be addressed.

In this paper, we report the specific complexation of **1** and **2** with four monosaccharides (D-glucose, D-mannose, D-galactose, and D-fructose) and four disaccharides (D-maltose, D-cellobiose, D-lactose, and D-saccharose).



A pair of chiral atropisomers formed from **2** and saccharides

Specific complexation of 1 and 2 with saccharides



Complexation of 1 with mono- and disaccharides[16]

The mixtures of saccharide molecules and reference compound **3** did not give any perceptible CD band in the UV region (above 220 nm). In the presence of **1**, in contrast, certain saccharide molecules gave rise to a CD band at about 275 nm (Figure 1), which was almost the same wavelength as the absorption maximum. Among mono- or disaccharides tested herein, glucose, mannose, galactose, maltose, cellobiose, and lactose were CD-active. In particular, glucose gave a largest CD band. Only the complex with D-galactose gave a positive CD band among D-saccharides tested herein. On the other hand, fructose and saccharose were CD-silent. As shown in Figure 1, D and L isomers afforded symmetrical CD spectra (θ_{275} −5300 for D-glucose and +5300 for L-glucose). To specify where **1** forms covalent bonds with D-glucose we examined methyl α-D-glucoside, D-xylose, and D-glucose-6-phosphate as reference compounds for D-glucose. It was found that none of them are CD-active. The results indicate cis-1,2-diol and trans-4-OH·5-CH_2OH are essential for complexation with **1**. The ^{1}HNMR spectrum of the **1**·D-glucose complex also supports the structure in Figure 2. Thus, cis-1,2-diol and

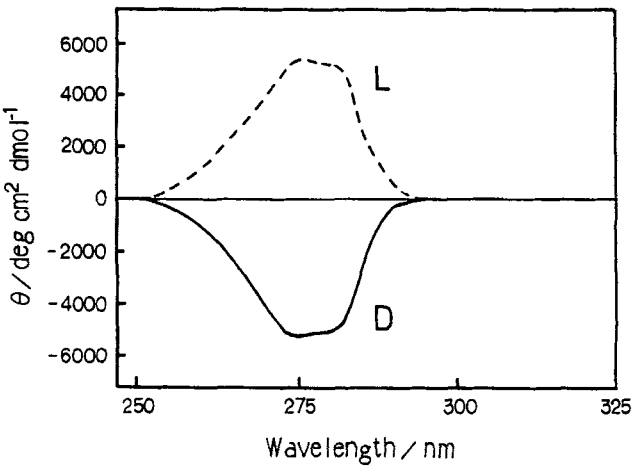


Figure 1 CD spectra for D-glucose (solid line) and L-glucose (dashed line): [glucose] = 0.10 mol dm^{-3}, [**1**] = 2.00 × 10^{-3} mol dm^{-3}, pH 11.3 with 0.10 mol dm^{-3} of Na_2CO_3, 25°C.

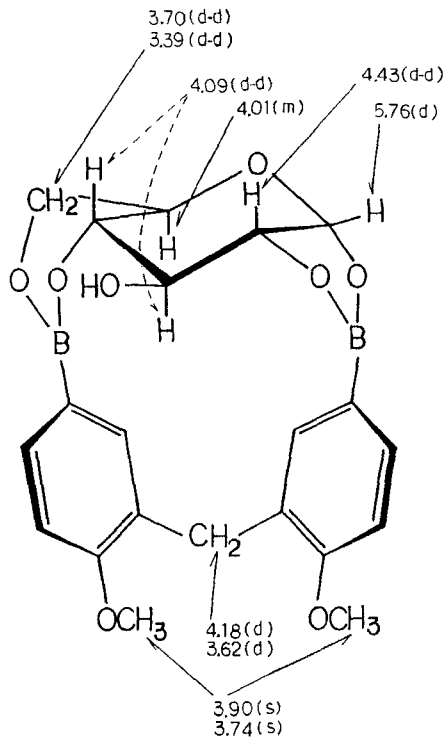


Figure 2 Structure of the **1**·α-D-glucopyranose complex. The numbers indicate chemical shifts of the ^{1}H NMR spectrum. The splitting pattern is shown in the parentheses. One of the 3-H and 4-H protons is overlapped with HDO, so that the peak at 4.09 ppm is assigned either to 3-H or to 4-H. The J_{HH} = 3.72 Hz for 1-H and 2-H indicates that these two protons are fixed to a gauche conformation (i.e., D-glucopyranose adopts the α-form).

Table 1 Absorption and CD spectra of **1** and its disaccharide complexes and their association constants (K)[a]

Saccharide	Absorption maximum nm	CD maximum $\lambda([\theta])$ nm (deg cm^2 dmol^{-1})	K dm^3 mol^{-1}
D-Glucose	274	275 (−5300)	19000
D-Mannose	272	274 (−400)	60
D-Galactose	273	276 (+410)	2200
D-Fructose	274	silent	—
D-Maltose	275	275 (−2400)	100
D-Cellobiose	275	275 (−2000)	80
D-Lactose	275	275 (−1200[b])	15
D-Saccharose	275	silent	—

[a] [1] = 2.00 × 10^{-3} mol dm^{-3}, [D-glucose] = (0.5–5.00) × 10^{-3} mol dm^{-3}, [other saccharides] = 1.00 × 10^{-3}–0.1 mol dm^{-3}, 25°C, pH = 11.3 with 0.1 mol dm^{-3} Na_2CO_3. [b] An upper limit of the solubility of D-lactose is 0.20 mol dm^{-3}, where 75% of D-lactose exists as the complex and $\theta_{obsd} = -900$ deg cm^2 dmol^{-1}. The value in this table is calculated assuming the formation of the 100% complex.

trans-4-OH · 5-CH_2OH are prerequisites for the formation of CD-active complexes.

From plots of θ vs. [saccharide] we determined stoichiometry and association constants (K). The results are summarized in Table 1. It was found that all of the CD-active complexes with **1** have 1:1 stoichiometry.

Why does only **1** afford the CD-active complexes? Compound **3** should also form complexes with saccharides, but they are CD-silent. Compound **1** can form a cyclic structure through two-site binding (as shown in Figure 2). Conceivably, the ring structure would freeze the molecular motion of chromophoric benzene moieties in **1**. This situation is favorable for the appearance of a CD band.[17] The explanation is compatible with the fact that the complexes with mannose and galactose afford smaller K values than that with glucose, probably because of the smaller binding ability to form a cyclic structure.

Complexation of 2 with mono- and disaccharides[18]

Compound **4** was, of course, CD-silent whereas a distinct CD band appeared in the presence of D-maltose (Figure 3). The split CD band which crosses the $[\theta] = 0$ line at 210 nm (ref. $\lambda_{max} = 207$ nm in the absorption spectrum) is ascribed to an exciton coupling. The negative sign for the first Cotton effect (223 nm) and the positive sign for the second Cotton effect (201 nm) indicate that the two dipoles along the phenylboronic acid molecular axis are oriented in a chiral, anti-clockwise direction when they interact in the excited state.[17] These findings reveal that when **2** forms a complex with D-maltose, the two dipoles favorably adopt (*S*)-chirality. Very interestingly, D-cellobiose induced the positive sign for the first Cotton effect whereas D-lactose induced the negative sign for

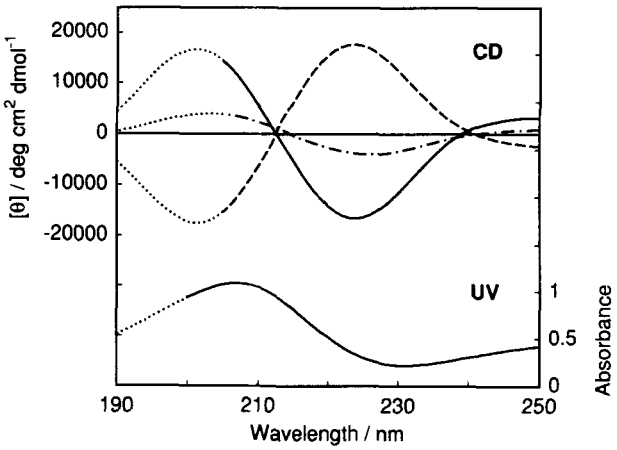


Figure 3 Absorption spectrum of **2** (5.0 × 10^{-3} mol dm^{-3}) and CD spectra of **2** (5.0 × 10^{-3} mol dm^{-3})·disacchraide complexes: —— D-maltose (5.0 × 10^{-3} mol dm^{-3}), --- D-cellobiose (5.0 × 10^{-3} mol dm^{-3}), —·— D-lactose (5.0 × 10^{-3} mol dm^{-3}), 25°C, pH = 10.5 with 0.1 mol dm^{-3} carbonate buffer. At 190–200 nm region the precise CD measurement was difficult because of the strong background (shown as dotted lines).

the first Cotton effect although the maximum (or minimum) wavelength for the second Cotton effect could not be determined precisely because of the strong background noise.[19] The results imply that the complexes with D-cellobiose and D-lactose employ (*R*)- and (*S*)-chirality, respectively. On the other hand, D-saccharose was totally CD-silent.

Compound **2** was designed so that it could selectively bind disaccharides. Because of the difficulty in the 'fine-tuning', the distance between the two boronic acids is slightly shorter than that between 1,2-diol and 4′-OH · 5′-CH_2OH in disaccharides. We expected that **2** would scarcely show affinity toward monosaccharides. Contrary to our expectation, D-glucose and D-galactose behaved as CD-active monosaccharides although the $[\theta]$ values were smaller by one order of magnitude than those for disaccharides. D-Mannose and D-fructose were CD-silent (Figure 4).

We estimated stoichiometry and association constants of these complexes from plots of θ vs. [disaccharide]. The results are summarized in Table 2. It was found that all of the CD-active complexes with **2** have 1:1 stoichiometry. We also tried to estimate the stoichiometry for the complexes with monosaccharides. However, the continuous variation plots did not result in a clear maximum and the plot showed a concentration dependence. This reveals that complex formation with these monosaccharides is not a simple A + B ⇄ A · B type equilibrium.

Then, what is the origin of the chirality in exciton couplings observed for **2**·disaccharide complexes? Through the studies on the complex formation of monosaccharides with **1** and two-phase solvent-extraction of monosaccharides with phenylboronic

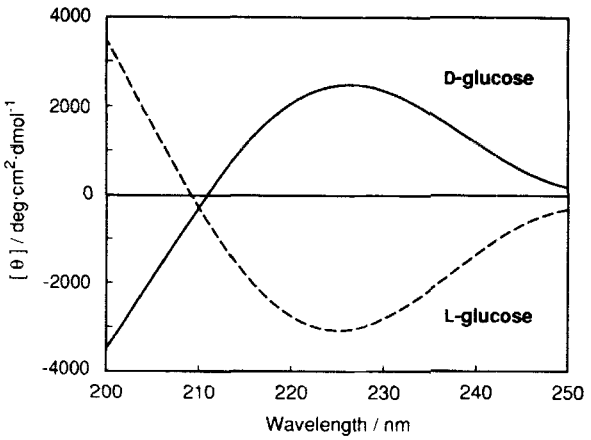


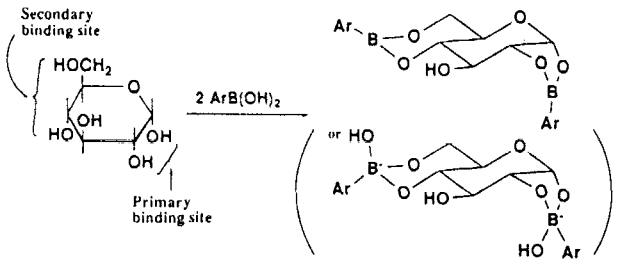
Figure 4 CD spectra of **2** (5.0×10^{-3} mol dm^{-3})·monosaccharide complexes: D- and L-glucose (5.0×10^{-3} mol dm^{-3}), 25°C, pH = 10.5 with 0.1 mol dm^{-3} carbonate buffer.

Table 2 Absorption and CD spectra of **2** and its disaccharide complexes and their association constants (K)[a]

	Absorption maximum	*CD maximum*	*K*
Disaccharides	*nm*	*λ([θ]) nm (deg cm² dmol⁻¹)*	*dm³ mol⁻¹*
D-Maltose	207	223 (−17000) 201[b]	200
D-Cellobiose	207	224 (19000) 203[c]	50
D-Lactose	207	226 (−4000) —[d]	400
D-Saccharose	207	silent	—

[a] 25°C, pH = 10.5 with 0.1 mol dm^{-3} carbonate buffer.
[b] $[\theta]_{max}$ is positive, but $[\theta]$ could not be determined precisely.
[c] $[\theta]_{max}$ is negative, but $[\theta]$ could not be determined precisely.
[d] $[\theta]_{max}$ is positive, but $[\theta]$ and λ_{max} could not be determined precisely.

acid derivatives we in fact confirmed that the primary binding site is the cis-1,2-diol moiety and the secondary binding site is the trans-4-OH·5-CH_2OH moiety (Scheme 1).[16,20] In complexation with D-maltose and D-cellobiose the cis-1,2-diol moiety is used as the primary binding site and the trans-4′-OH·5′-CH_2OH moiety is used as the secondary binding site. Except these diol groups, in fact, there exists no diol group that satisfies the above-mentioned requirements for complexation with boronic acids. In D-lactose, on the other hand, there are two possible secondary binding sites, cis-3′,4′-diol and trans-4′-OH·5′-CH_2OH. In D-saccharose, there is no cis-1,2-diol which can serve as a primary binding site. These binding modes are further supported by the following findings: (i) when **4** was used instead of **2**, the CD spectral band was not observed for these disaccharides and (ii) D-maltose-1-phosphate was CD-silent even in the presence of **2**. These findings consistently support the view that the CD-activity is due to the formation of a ring structure



Scheme 1

by the two-point binding between **2** and disaccharides, which results in the chiral immobilization of the diphenyl moiety.

To further confirm the binding modes in Scheme 1, we computed the heat of formation for five isomers possible in the complex between D-glucose and phenylboronic acid (MOPAC ver 6.0, AM1 Hamiltonian). The boron atoms were assumed to adopt sp^3-orbitals. As shown in Figure 5, the most stable complex is that formed via trans-4-OH·5-CH_2OH diol (−417.1 kcal mol^{-1}). This complex includes a six-membered ring which features smaller van der Waals repulsion among C-H and C-C bonds than a five-membered ring. Among four isomers having a five-membered ring, the most stable complex is that formed via α-cis-1,2-diol (−413.9 kcal mol^{-1}). In this complex, van der Waals repulsion expected for the five-membered ring is somewhat relaxed by the neighbouring oxygen atom in the D-glucose ring. Besides this, it seems from the result that these five-membered rings of boronate esters prefer a 'coplanar' form to a 'envelope' form. In the most stable complex a five-membered ring can adopt a coplanar form by the conformational change of a glucopyranose ring. But the other three complexes cannot adopt a coplanar form by the conformational change of a glucopyranoside ring. These results also support the binding modes illustrated in Scheme 1. We thus tried to estimate the relative stability between (*R*)- and (*S*)-chirality of the **2**·D-maltose complex on the basis of a computational method.

Figure 6 shows the energy-minimum structures for the cyclic **2**·D-maltose complex estimated by the semiempirical molecular orbital calculation (MOPAC ver. 6.0, AM1 Hamiltonian). Figure 6A indicates the complex with (*R*)-chirality with the dihedral angle of 87.4°, whereas Figure 6B indicates the complex with (*S*)-chirality with the dihedral angle of −67.7°. It is seen from Figure 6 that two pyranose rings in D-maltose adopt a regular chair conformation. In Figure 6A the dihedral angle is almost close to a right angle, so that the distances from 2-H in **2** to 5-H and 6-H in D-maltose are short and may cause steric repulsion. In Figure 6B, on the other hand, the dihedral angle is significantly smaller than that in Figure 6A,

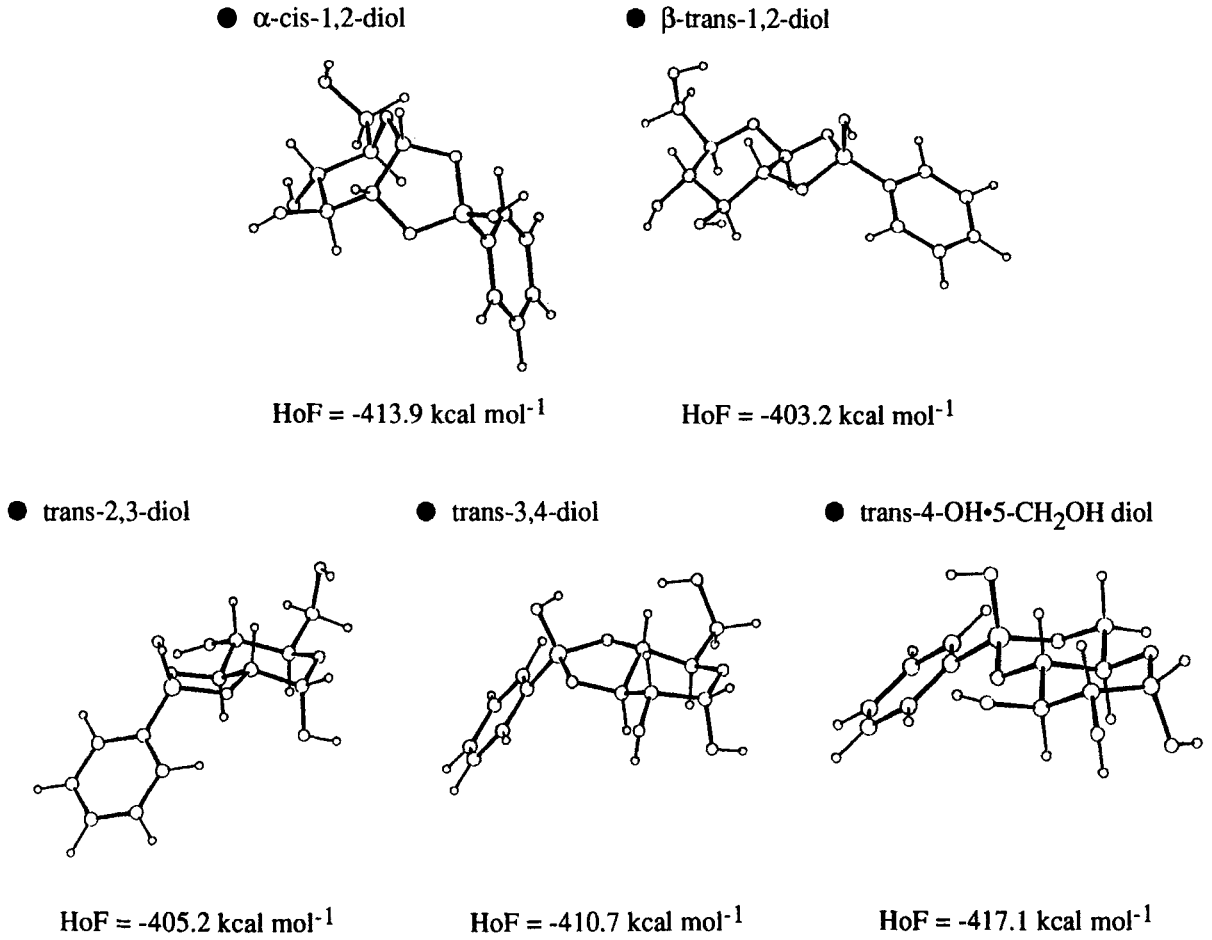


Figure 5 Calculated heat of formation (HoF) for five complexes formed from D-glucopyranose and phenylboronic acid.

so that such steric repulsion (if any) is expected only between 2-H in **2** and 3′-H in D-maltose. The heat of formation estimated for (*S*)-chirality (−719.6 kcal mol^{-1}) is smaller by 0.8 kcal mol^{-1} than that estimated for (*R*)-chirality (−718.8 kcal mol^{-1}). The observed CD spectrum with the first negative Cotton effect and the second positive Cotton effect is a sign of (*S*)-chirality and shows a good agreement with this theoretical prediction.

The superiority of (*R*)-chirality in the **2** · D-cellobiose and that of (*S*)-chirality in the **2** · D-lactose can be explained on the same basis. Very interestingly, we noticed a potential relationship lying between the CD sign and the disaccharide structure. The sole structural difference between D-maltose and D-cellobiose is the configuration of the glucoside linkage: D-maltose has the α-glucoside linkage while D-cellobiose has the β-glucoside linkage. Therefore, when the two boronic acids form covalent-bonds with 1,2-cis-diol and 4′-OH · 5′-CH_2OH the two phenyl rings in **2** should cross in an opposite way. This difference can lead to the opposite sign in the CD spectra. This explanation is extended to the CD sign of the **2** · D-lactose complex. In D-lactose 4′-OH is inversed from that in D-cellobiose. If the covalent-bond formation occurs at 3′,4′-cis-diol(this binding manner is favored because the distance between the two boronic acids is slightly shorter than that between 1,2-cis-diol and 4′-OH · 5′-CH_2OH), then two phenyl rings in the **2** · D-lactose complex should adopt the opposite orientation against those in the **2** · D-cellobiose complex. That is, the **2** · D-cellobiose complex shows (*R*)-chirality and the **2** · D-lactose complex shows (*S*)-chirality.

In contrast to the above-mentioned disaccharides, D-saccharose has no cis-1,2-diol although it has trans-4′-OH · 5′-CH_2OH which may serve as the secondary binding site. Thus, D-saccharose is unable to make the cyclic structure with **2** and to asymmetrically-immobilize the two phenyl rings. This is why D-saccharose is totally CD-silent.

CONCLUSIONS

It is well-known that boronic acids form stable complexes with diols.[21] The reaction occurs easily at

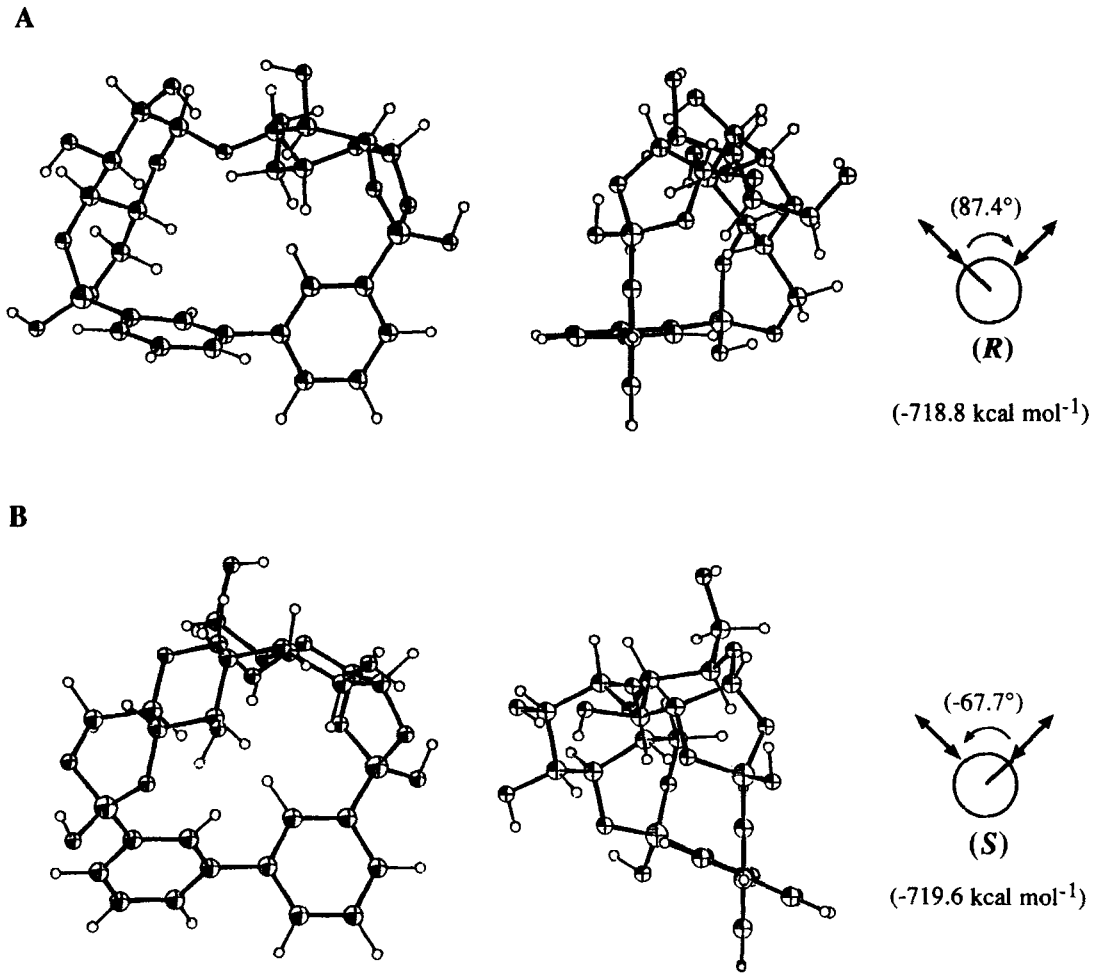


Figure 6 ORTEP views of the cyclic 2·D-maltose complex. The sp^3-orbital is adopted to boronic acids.

room temperature in an aqueous system. We here demonstrated that by the combination of this 'classical' reaction with CD spectroscopy sugar molecules can be easily detected and even the absolute configuration can be predicted. In particular, 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid and diphenyl-3,3′-diboronic acid used herein behaves as an excellent probe for monosaccharides and disaccharides, respectively. We believe that this concept is applicable not only to the detection of sugar molecules but also to the control of complex equilibria in sugar molecules and as a protecting method for selective modification of OH groups in sugar molecules.

REFERENCES AND NOTES

1 Fersht, A.R.; *Trends Biochem. Soc.* **1987**, *12*, 301.
2 Turner, D.H.; Sugimoto, N.; Kierzek, R.; Dreiker, D.S.; *J. Am. Chem. Soc.* **1987**, *109*, 3783 and references cited therein.
3 (a) Rebek, J. Jr.; Marshall, L.; Wolak, L.; Parris, K.; Killoran, M.; Askew, B.; Nemeth, D.; *J. Am. Chem. Soc.* **1985**, *107*, 7476. (b) Rebek, J. Jr.; Nemeth, D.; *Ibid.* **1986**, *108*, 5637. (c) Rebek, J. Jr.; Askew, B. Killoran, M.; Nemeth, D.; Lin, F.T.; *Ibid.* **1987**, *109*, 2426. (d) Rebek, J. Jr.; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 245.
4 (a) Hamilton, A.D.; van Engen, D.; *J. Am. Chem. Soc.* **1987**, *109*, 5035. (b) Chang, S.K.; Hamilton, A.D.; *Ibid.* **1988**, *110*, 1318. (c) Hamilton, A.D.; Pant, N.J.; *J. Chem. Soc., Chem. Commun.* **1988**, 765. (d) Goswami, S.; Hamilton, A.D.; *J. Am. Chem. Soc.* **1989**, *111*, 3425.
5 (a) Kelly, T.R.; Maguire, P.M.; *J. Am. Chem. Soc.* **1987**, *109*, 6549. (b) Kelly, T.R.; Zhao, C.; Bridger, G.J.; *Ibid.* **1989**, *111*, 3744.
6 (a) Etter, M.C.; Panunto, T.W.; *J. Am. Chem. Soc.* **1988**, *110*, 5896. (b) Etter, M.C.; Adsmond, D.A.; *J. Chem. Soc., Chem. Commun.* **1990**, 589.
7 Hedge, V.; Madhukar, P.; Madura, J.D.; Thummel, R.P.; *J. Am. Chem. Soc.* **1990**, *112*, 4549.
8 Bell, T.W. Liu, J.; *J. Am. Chem. Soc.* **1988**, *110*, 3673.
9 Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H.; *J. Am. Chem. Soc.* **1988**, *110*, 634.
10 Tanaka, Y.; Ubukata, Y.; Aoyama, Y.; *Chem. Lett.* **1988**, 1905.
11 Kano, K.; Yoshiyasu, K.; Hashimoto, S.; *J. Chem. Soc., Chem. Commun.* **1988**, 801.
12 Wulff, G.; Heide, B.; Helfmeier, G.; *J. Am. Chem. Soc.* **1987**, *108*, 1089.
13 Wulff, G.; Poll, H.-G.; *Makromol. Chem.* **1987**, *188*, 741.

14 For a comprehensive review see Wulff, G. *Pure Appl. Chem.* **1982**, *54*, 2093.
15 'The distance between the two boronic acids' represents that between the two boron atoms. The distance becomes 7.4 Å when two benzene rings are flat and two boronic acids adopt a syn conformation whereas it becomes 9.2 Å when two benzene rings are flat and two boronic acids adopt an anti conformation. 'The distance between 1,2-diol and 4'-OH · 5'-CH_2OH' represents that between the oxygen atom of 1-OH of a pyranose ring and the oxygen atom of 4'-OH of the another pyranose ring.
16 Tsukagoshi, K.; Shinkai, S.; *J. Org. Chem.* **1991**, *56*, 4089.
17 (a) Harada, N.; Nakanishi, K.; *Acc. Chem. Res.* **1972**, *5*, 257. (b) Idem.; In *Circular Dichroic Spectroscopy*, Tokyo Kagaku Dojin, Tokyo, **1982**.
18 Kondo, K.; Shiomi, Y.; Saisho, M.; Harada, T.; Shinkai, S.; *Tetrahedron* **1992**, *48*, 8239.
19 The clear exciton coupling for D-lactose was observed at [D-lactose] > 2.5×10^{-3} mol dm^{-3}.
20 Shinkai, S.; Tsukagoshi, K.; Ishikawa, Y.; Kunitake, T.; *J. Chem. Soc., Chem. Commun.* **1991**, 1039.
21 Fieser, L.F.; Fieser, M.; in *Reagents for Organic Synthesis*, John Wiley & Sons, New York, **1967**, p. 833.