Molecular Design of Highly Selective and Sensitive "Sugar Tweezers" from Boronic Acid-Appended μ-Oxo-bis[porphinatoiron(III)]s

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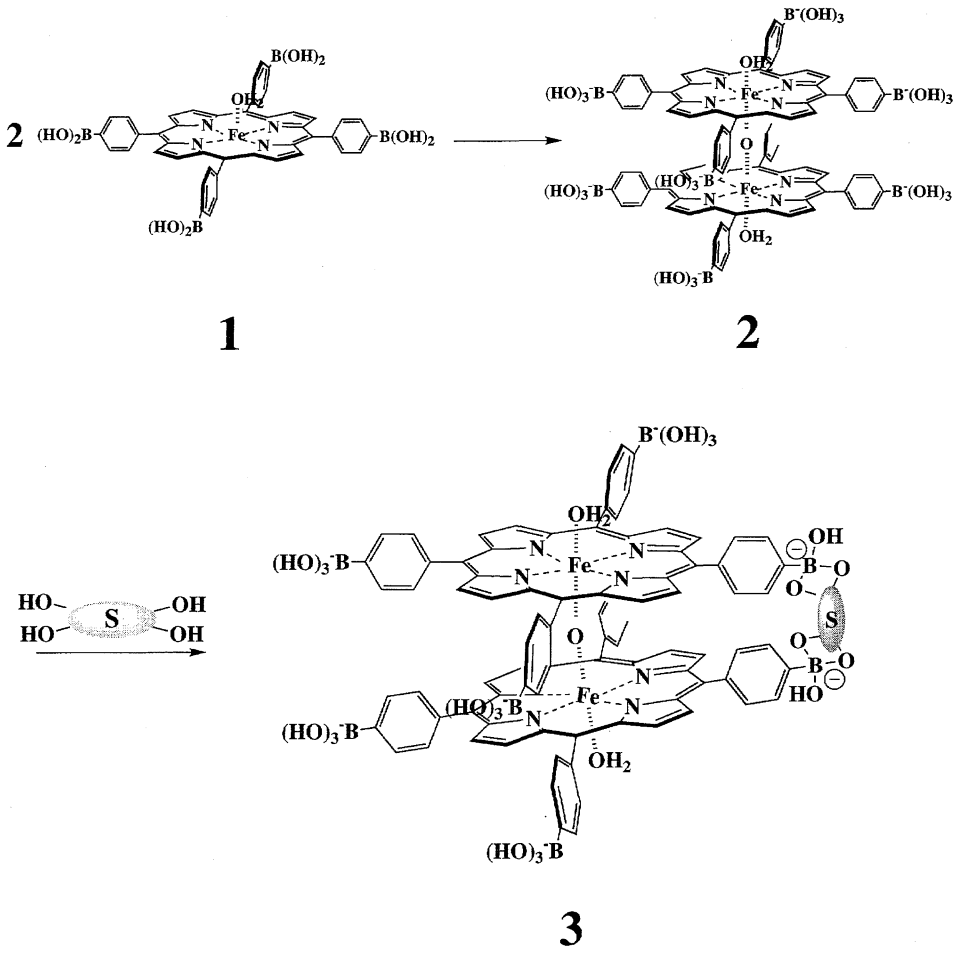
5, 10, 15, 20-Tetrakis[3- and 4-(dihydroxyboryl)phenyl]porphinatoiron(III)s (**1a** and **1b**, respectively) were synthesized and the saccharide-binding ability of their μ-oxo dimers was investigated. The saccharide-binding process with boronic acids can be conveniently monitored by CD spectroscopy. The μ-oxo dimer of **1b** with 4-(hydroxyboryl) groups can bind glucose and galactose among monosaccharides with extremely high selectivity and sensitivity (association constants 10^4—10^5 $dm^3\,mol^{-1}$), whereas that of **1a** with 3-(hydroxyboryl) groups shows only a weak affinity with these monosaccharides. A similar trend was also observed for disaccharides. The origin of the CD activity in **2b** can be ascribed to the formation of 1 : 1 μ-oxo dimer/saccharide complexes, in which two porphyrin rings are chirally bridged by one saccharide molecule. The CD sign is well-correlated with the absolute configuration of these saccharides. Thus, the present paper demonstrates that the μ-oxo dimer of **1b**, which is formed in a self-assembled manner in aqueous alkaline solution, acts as an excellent pair of artificial "sugar tweezers".

The molecular design of artificial receptors which can precisely and specifically discriminate between guest molecules has become a very active area of endeavor. In most reported synthetic receptors, hydrogen-bonding interactions with a complementary donor–acceptor relationship play a central role.[1—3] It is shown, however, that the hydrogen-bonding interactions are very effective only in aprotic solvents, but less effective for recognition of guests (such as sugars) soluble only in aqueous solutions. The inefficient binding ability of such hydrogen-bond-based synthetic receptors prompted us to search for an alternative binding force useful in an aqueous system. Our group[4] as well as other researchers[5—8] have thus started to exploit the interactions of arylboronic acids and saccharides for the development of receptor sites for saccharide detectors. We previously showed that boronic acid-appended porphyrins act as very useful spectroscopic sensors to detect saccharide in water by fluorescence and also to predict the absolute configuration by circular dichroism (CD).[9,10] Through these studies it has become clear that one must manipulate two boronic acid moieties in an appropriate spatial position in order to achieve successful two-point interrogation of a specific saccharide guest.[9,11] In these systems, only when two boronic acid moieties are intramolecularly bridged by a saccharide does the specific saccharide selectivity become observable and the resultant saccharide-containing macrocycles become CD-active.[4] Here, it occurred to us that in order to arrange two boronic acid-appended porphyrins in an appropriate spatial position, a μ-oxo dimer (**2**) of porphinatoiron(III) (**1**) would have a great potential (Scheme 1): The μ-oxo dimer is formed stably in basic aqueous solution[12] where the boronic acid–saccharide complex is also formed stably.[4—9,11] Furthermore, the distance between two porphyrin planes (3.8 Å)[13] is comparable with the molecular size of monosaccharides (3.0 Å) (Chart 2). With these objects in mind we synthesized **1a** and **1b** (Chart 1). This paper demonstrates that the μ-oxo dimer **2b** can bind glucose and galactose (intramolecularly as in **3b**) very selectively and sensitively among many monosaccharides and their absolute configuration is readily determined from the sign of the CD spectra (Chart 3).[14]

Results and Discussion

Formation of μ-Oxo Dimers. To confirm the formation of μ-oxo dimers, the absorption spectra were measured as a function of medium pH (Fig. 1A for **1b**: The spectra for **1a** are basically similar to Fig. 1A). A plot of A_{418} (Soret band) vs. pH was increased from pH 9.0 and saturated at pH 10.5 with $\varepsilon_{418} = 78000$ $dm^3\,mol^{-1}\,cm^{-1}$ for **1a** and 77000 $dm^3\,mol^{-1}\,cm^{-1}$ for **1b** (Fig. 1B). The species formed at pH 10.5 gave a Fe–O–Fe stretching band at 850 cm^{-1} in IR spectroscopy ($[\mathbf{1}] = 1.0\times10^{-3}$ $mol\,dm^{-3}$). This value is comparable with those reported for the porphinatoiron(III) μ-oxo dimers.[15] Furthermore, the species present in acidic media were ESR-active (characteristic of porphinatoiron(III)), whereas the species became ESR-silent at pH 10.5 (characteristic of the μ-oxo dimers). These lines of spectral evidence support the view that **1a** and **1b** are converted to the μ-oxo dimers at pH 10.5.

Qualitative Screening of the Affinity with Mono- and Disaccharide. Examination of the absorption spectra of **2** at pH 10.5 in the absence and the presence of saccharides showed that they are not much affected by saccharide addition. It is known that, when saccharides react intramolecularly with two boronic acid moieties to form saccharide-containing chiral macrocycles, strong exciton-coupling bands appear in CD spectroscopy.[4] By using this method, we



Scheme 1.

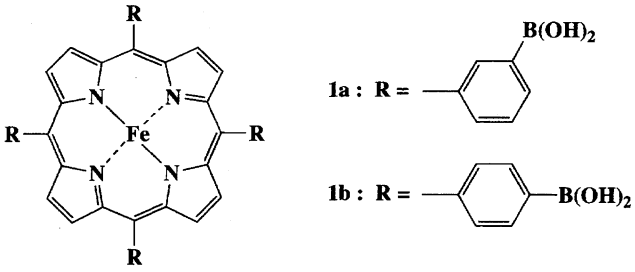


Chart 1. Structure of **1a** and **1b**.

screened many mono- and disaccharides to know whether the μ-oxo dimers become CD-active. With **2a**, the weak CD spectrum was observed at Soret band region only for glucose among 7 monosaccharides tested herein (Fig. 2).[16] With **2b**, on the other hand, the strong exciton-coupling bands appeared only in the presence of glucose and galactose (Fig. 3). Presumably, the two porphyrin rings in the **2a**·monosaccharide complexes cannot be immobilized so rigidly as to become CD-active, because the slight rotation in the *meso*-phenyl groups readily changes the distance between two boronic acid moieties. In **2b**, in contrast, such a distance change cannot be induced by the rotation of the *meso*-phenyl groups. Hence, the monosaccharide (i.e., glucose and galactose) can firmly suppress the porphyrin ring rotation and orientate them in an asymmetric manner. This is the origin of the strong exciton-coupling band observed for the **2b** system. The CD intensity could be detected even for the 10^{-5} mol dm^{-3} order of glucose and galactose. One can thus conclude that ***2b** acts as a highly selective and sensitive pair of "sugar tweezers" for glucose and galactose.*

Next, we applied **2a** and **2b** to 10 disaccharides.[17] With **2a**, the believable CD spectrum was obtained only from maltose (Fig. 4). Since disaccharides are conformationally more flexible owing to the central glycoside linkage than monosaccharides, they seem to have little ability to immobilize two porphyrin rings in **2a**. With **2b**, the stronger CD bands were observable for lactose, cellobiose and saccharose (but not for maltose: Fig. 5). The CD spectra for cellobiose and sucrose cross the $[\theta]=0$ line around the λ_{max} of the Soret band (418 nm). One may thus regard these spectra as consisting of the exciton-coupling bands (although somewhat unsymmetrical). From the examination of a disaccharide structure-CD sign correlation, we can identify the following characteristics: (i) maltose (4-*O*-α-D-glucopyranosyl-β-D-glucopyranose) has a positive exciton-coupling band with **2a**, whereas cellobiose (4-*O*-β-D-glucopyranosyl-α-D-glucopyranose) has a negative exciton-coupling band with **2b**, and

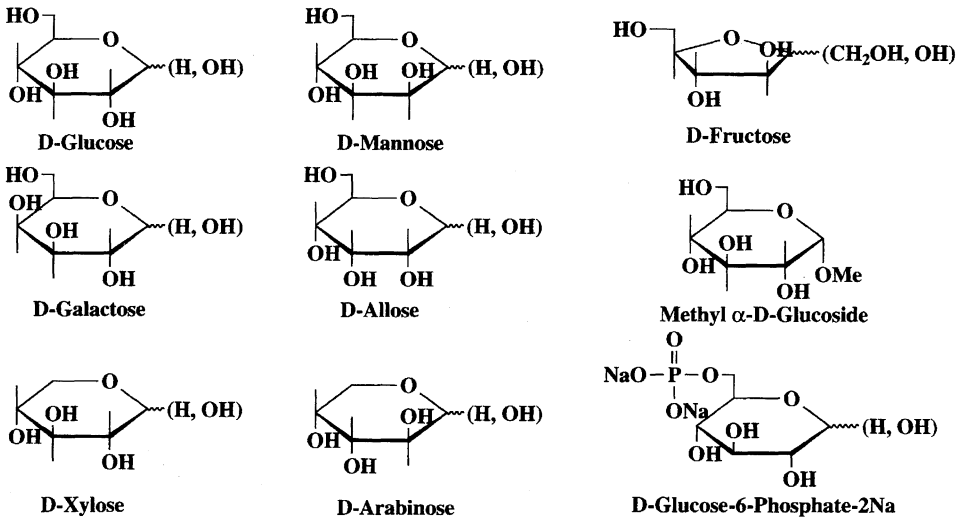


Chart 2. Monosaccharides.

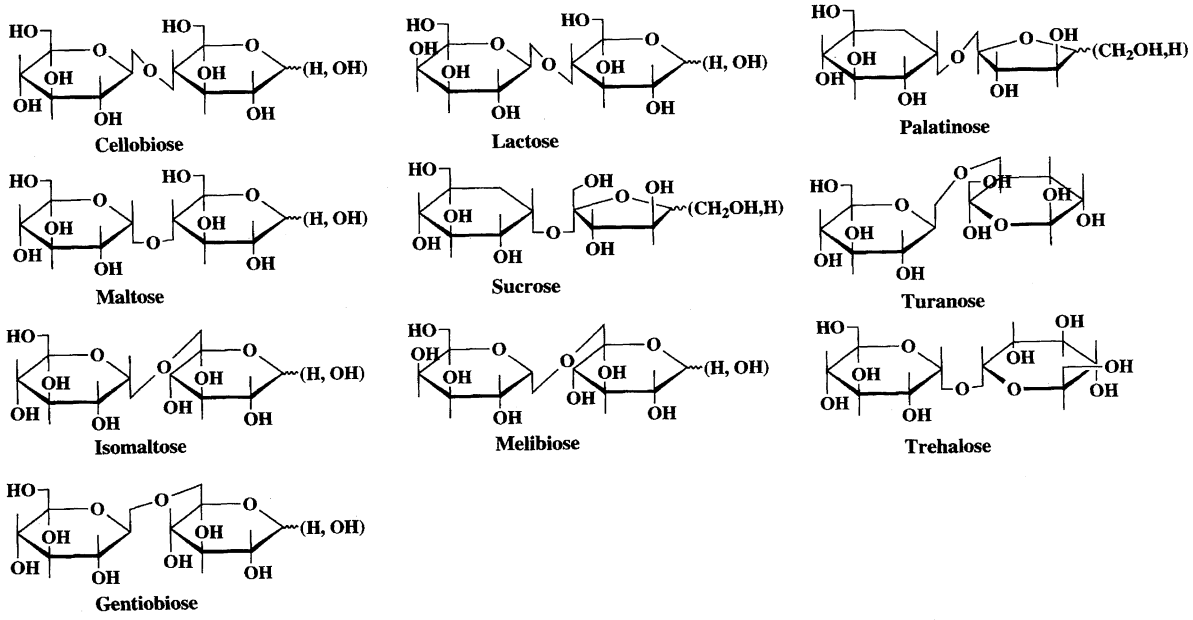


Chart 3. Disaccharides.

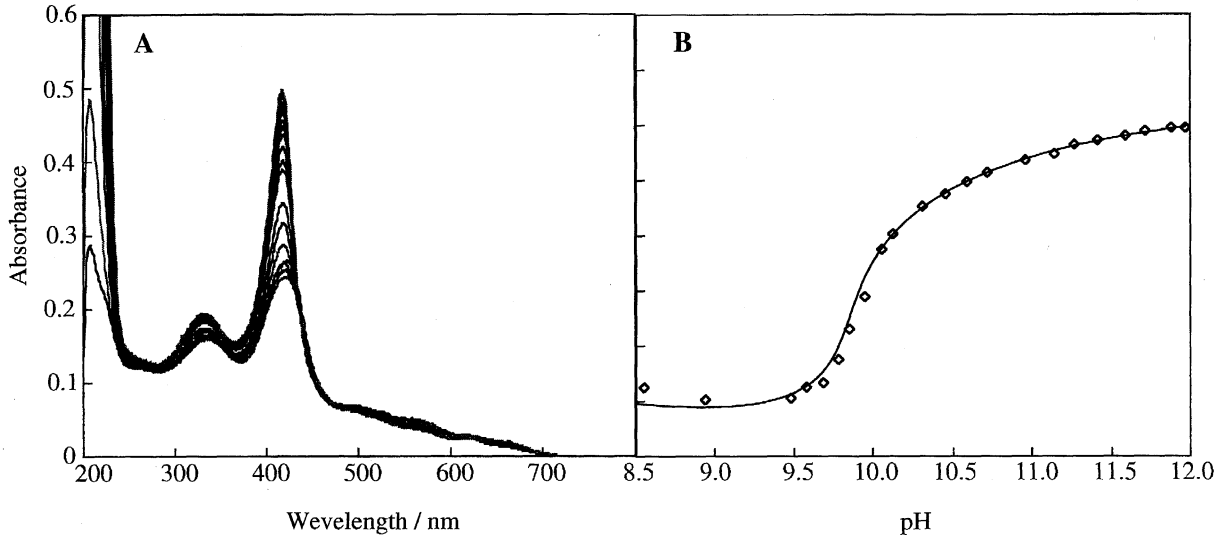


Fig. 1. Absorption spectra (A) and a plot of A_{418} vs. pH (B) for **1b**: [**1b**] = 1.00×10^{-5} mol dm^{-3}, MeOH : water = 1 : 300 v/v, 25 °C. The pH was adjusted with HCl–NaOH.

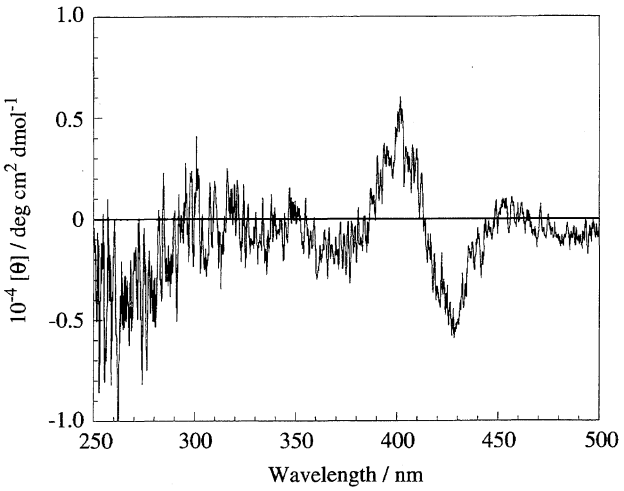


Fig. 2. Weak CD spectrum observed for a **2a**+D-glucose system: [**1a**] = 5.0×10^{-6} mol dm^{-3}, [D-glucose] = 5.00×10^{-3} mol dm^{-3}, 25 °C, MeOH : water = 1 : 300 v/v, pH 10.5 with 50 mmol dm^{-3} carbonate buffer.

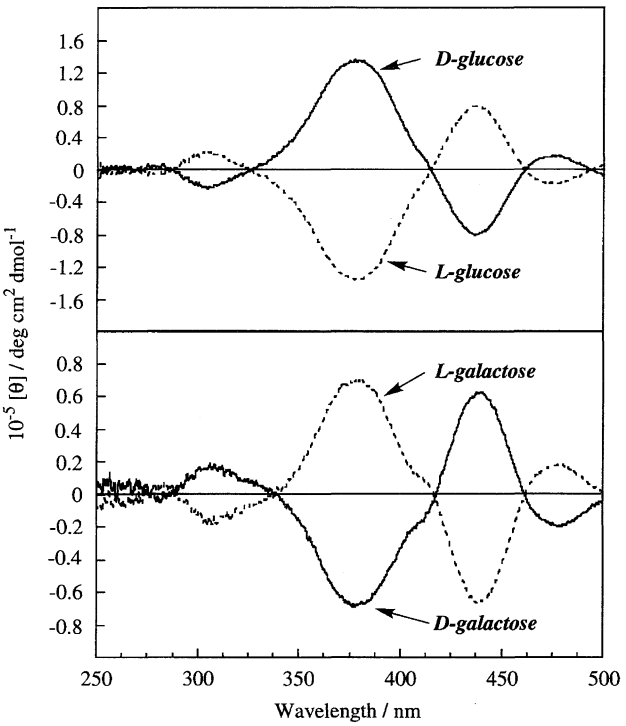


Fig. 3. Strong CD spectra with exciton-coupling bands observed for **2b**+D- and L-glucose and **2b**+D- and L-galactose systems. The measurement conditions are the same as those recorded in a caption to Fig. 2.

(ii) the CD spectrum for a **2a**+maltose system is very similar to that for a **2b**+sucrose system. Because of the flexible nature of disaccharides, however, it is difficult to image the stable complex structure. Hence, it is not yet clear how these CD signs correlate with the disaccharide structure.

Quantitative Analysis of the Complexation Mode with Glucose and Galactose. To obtain quantitative insights into the complexation mode, we estimated the stoichiometry of the complexes by a continuous variation plot[18] of

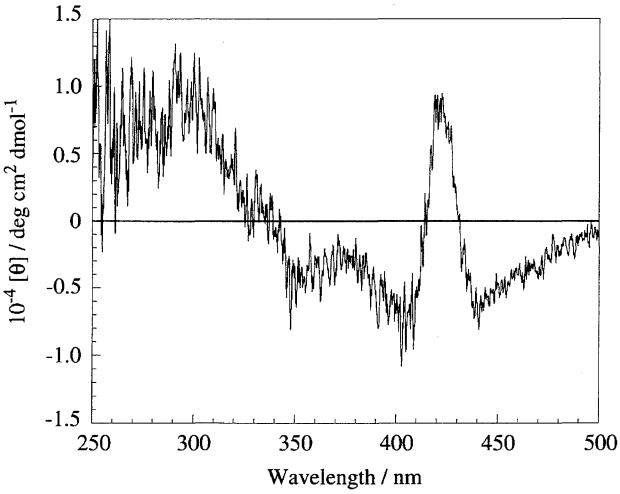


Fig. 4. Weak CD spectrum observed for a **2a**+maltose system. The measurement conditions are the same as those recorded in a caption to Fig. 2.

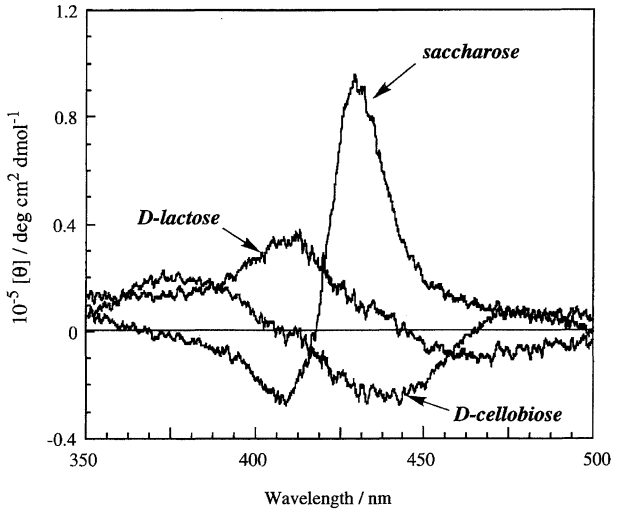


Fig. 5. Moderately strong CD spectra observed for **2b**+lactose, **2b**+cellobiose, and **2b**+sucrose systems. The measurement conditions are the same as those recorded in Fig. 2.

CD intensity (θ_{obs} at 380 nm) vs. [**2b**]/([**2b**]+[D-glucose]) (Fig. 6). A maximum appeared at 0.5. D-Galactose also gave the maximum at 0.5. The results indicate that, even though **2b** has eight boronic acid moieties, only two boronic acid moieties are used to form the 1 : 1 **2b**·saccharide complexes: That is, this system features strong "negative allosterism" in the saccharide-binding process. Judging from the previous examples,[19] the boronic acid-binding sites are 1,2-diol and 5,6-diol in glucofuranoside or 1,2-diol and 4,6-diol in glucopyranoside. In either case, examination of CPK molecular models reveals that, when two boronic acid moieties react with these two diol groups, they must get close to each other, and the Fe–O–Fe bond angle is deformed to 150° from the regular 180°. In ESR spectroscopy of the **2b**·D-glucose complex ([**2b**] = 5.0×10^{-4} mol dm^{-3}, [D-glucose] = 5.0×10^{-4} mol dm^{-3}, pH 10.5 with 50 mmol dm^{-3} carbonate buffer,

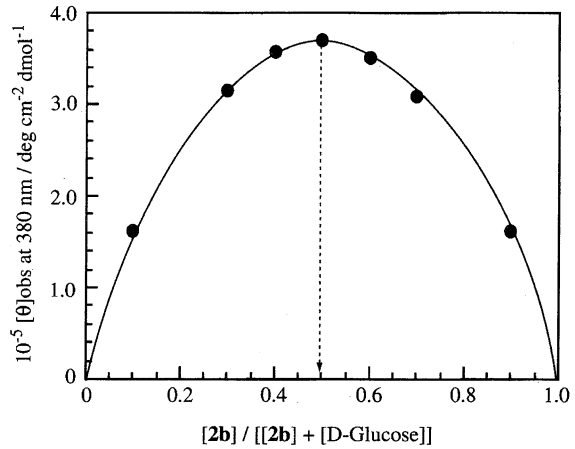


Fig. 6. Continuous variation plot of CD spectra of **2b** (5.00×10^{-6}—4.50×10^{-5} mol dm^{-3}) in the presence of D-glucose (5.00×10^{-6}—4.50×10^{-5} mol dm^{-3}), 25 °C, MeOH : water = 1 : 300 v/v, pH 10.5 with 50 mmol dm^{-3} carbonate buffer. The unit of the ordinate is the CD intensity difference between the presence and the absence of D-glucose.

77 K), the high spin Fe^{III} signal with $S=5/2$ was observed ($g=2.28$ and 6.04). As a result, the distance between two boronic acid moieties in the remaining three pairs becomes too long to complex the second saccharide intramolecularly.

It is now clear that the origin of the CD activity is related to the chiral immobilization of two porphyrin rings in **2b** by the saccharide bridging. The fact that **2b** in the presence of D-glucose-6-phosphate or methyl α-D-glucoside, which has only one boronic acid-binding site and therefore cannot bridge two porphyrin rings, is CD-silent also supports this proposal. From plots of CD intensity (θ_{obs} at 380 nm) vs. [saccharide] (Fig. 7) we estimated the association constants (K_{ass}) to be 1.51×10^5 dm^3 mol^{-1} for D-glucose and 2.43×10^4 dm^3 mol^{-1} for D-galactose (Table 1). *These values are the largest among those for artificial saccharide receptors and one to two orders of magnitude greater than those reported so far.*[4,9] The results clearly indicate that μ-oxo dimers provide an excellent platform for designing boronic acid-based saccharide receptors.

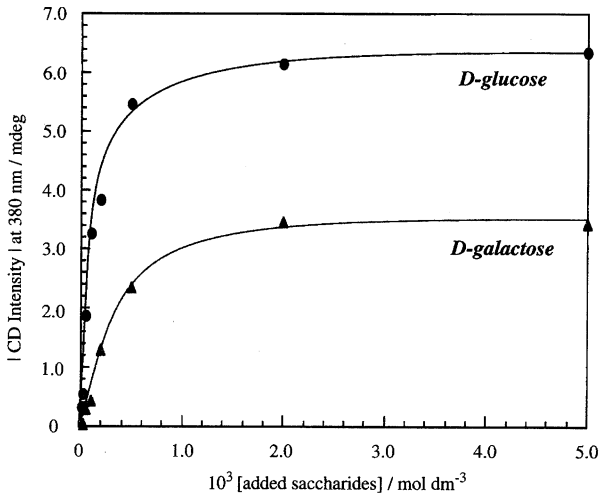


Fig. 7. Plots of the CD intensity for **2b**·D-glucose and **2b**·D-galactose complexes against [added saccharide] : [**2b**] = 5.00×10^{-6} mol dm^{-3}, 25 °C, MeOH : water = 1 : 300 v/v, pH 10.5 with 50 mmol dm^{-3} carbonate buffer.

Table 1. Assosiation Constants of Sugars with **2b**

Sugar	Association constant K_{ass} (dm^3 mol^{-1})
D-Glucose	1.51×10^5
D-Galactose	2.43×10^4

In order to demonstrate high "selectivity" of D-glucose vs. other saccharides, we examined the influence of the coexistence of other saccharides on the CD intensity of the **2b**·D-glucose complex (Fig. 8). We chose D-mannose, D-allose, and D-galactose (epimers of D-glucose) as competing saccharides. D-Galactose which has the 1/6 K_{ass} of that for D-glucose can compete with D-glucose to affect the CD intensity even at the low D-galactose concentration. In contrast, the CD intensity was little affected by added D-mannose and D-allose up to [added saccharide]/[D-glucose] = 100. The results indicate that **2b** possesses very high D-glucose selectivity and is useful as a D-glucose sensor even in the presence of these epimeric saccharides (except D-galactose).

Finally, we discuss the origin of the saccharide selectivity and the correlation between the absolute configuration and the CD sign. It is a controversial and often troublesome problem to clarify which form (furanose or pyranose) is immobilized by two boronic acid moieties.[19] In the present system this problem is not yet solved because the presence of Fe^{III} induces the fatal line-broadening in ^{1}H NMR spectroscopy. In either case, however, examination of CPK molecular models reveals that only glucose and galactose can form the intramolecular complexes with two boronic acid moieties in

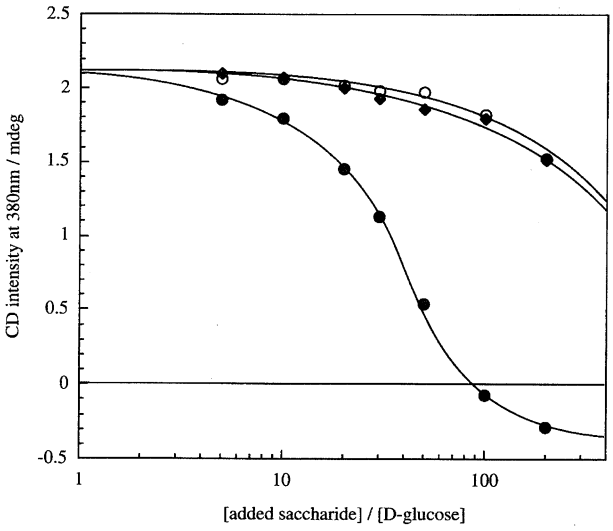


Fig. 8. Semilogarithmic plots of the CD intensity for **2b**·D-glucose complex against [added saccharide]/[D-glucose]: [**2b**] = 5.00×10^{-6} mol dm^{-3}, [D-glucose] = 1.00×10^{-4} mol dm^{-3}, 25 °C, MeOH : water = 1 : 300 v/v, pH 10.5 with 50 mmol dm^{-3} carbonate buffer; —●— D-galactose, —○— D-mannose, —◆— D-allose.

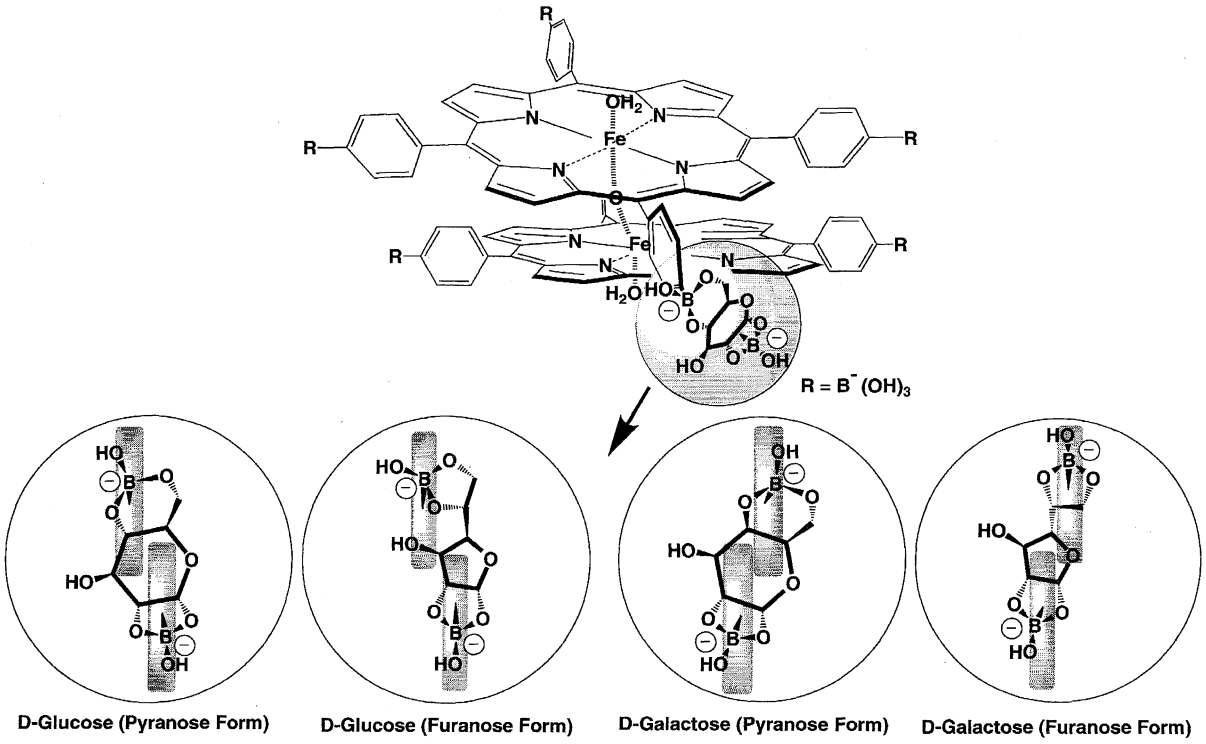


Fig. 9. Chiral twisting of two porphyrin rings by a saccharide (D-glucose or D-galactose).

2b, using 1,2-diol and 4,6-diol (in pyranose: 5,6-diol instead of 4,6-diol in furanose):[19] The use of 1,2-diol and 3,4-diol in galactose is sterically impossible because the distance is too short to bridge two porphyrin rings in **2b**. As shown in Fig. 3, CD spectra of glucose and galactose show the very interesting similarities: i. e., The CD spectrum of the D-glucose complex is symmetrical to that of the L-glucose complex but very similar to that of the L-galactose complex. Likewise, the CD spectrum of the D-galactose complex is symmetrical to that of the L-galactose complex but very similar to that of the L-glucose complex. The sole difference in the absolute configuration between glucose and galactose is the configuration of 4-OH. This implies that the absolute configuration of 4-OH decisively controls the orientation of two porphyrins. As shown in Fig. 9, D-glucose bridges two boronic acid moieties to twist porphyrins in a clockwise direction, whereas D-galactose bridges two boronic acid moieties to twist porphyrins in a anti-clockwise direction (regardless of the pyranose or furanose problem). The binding mode in Fig. 9 reasonably explains why the CD spectrum of the D-glucose complex is symmetrical to that of the D-galactose complex.

Conclusions. In conclusion, the present paper demonstrates that a highly selective and sensitive pair of "sugar tweezers" can be designed utilizing the self-assembling nature of bis[prophinatoiron(III)]s to form the μ-oxo dimers. The largest association constants achieved so far (10^4—10^5 $dm^3\ mol^{-1}$) even exceed those of enzymes specific to these saccharides.[20] The results suggest that further potential applications and extensions of the present system are possible, e. g., to sensitive sugar sensing, porphyrin-mediated photo- and redox reactions, selective adsorption and transport of sugars in the membrane system.

Experimental

Materials. 5, 10, 15, 20-Tetrakis[4-(dihydroxyboryl)phenyl]porphine (**4b**) was synthesized according to the method in a reference[9b] and identified by IR and ^{1}H NMR spectral evidence and elemental analysis.

5, 10, 15, 20-Tetrakis[3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl]-21*H*,23*H*-porphine (5a). A propionic acid solution (70 ml) containing 1,3-dioxa-2-(3-formylphenyl)-5,5-dimethylborinane (3.00 g, 9.86 mol) was stirred at 80 °C. To this solution was added pyrrole (0.70 ml, 9.86 mmol) and the solution was refluxed for 2 h. The solvent was evaporated and the oily residue was crystallized from acetone. The product mixture was purified by column chromatography (silica gel, chloroform : methanol = 30 : 1 v/v): Yield 1.5%, mp (decomp)> 300°C; ^{1}H NMR ($CDCl_3$; 27 °C) $\delta_H = -2.78$ (2H, s, NH of pyrrole), 1.07 (24H, s, CH_3), 3.81 (16H, s, CH_2), 7.73 (4H, t, ArH), 8.17 and 8.25 (8H, each d, ArH), 8.65 (4H, s, ArH), 8.81 (8H, s, CH of pyrrole). Found: C, 72.28; H, 6.45; N, 5.33%. Calcd for $C_{64}H_{66}B_4N_4O_8$: C, 72.35; H, 6.26; N, 5.27%.

5, 10, 15, 20-Tetrakis[3-(dihydroxyboryl)phenyl]-21*H*,23*H*-porphine (4a). Compound **5a** (40 mg, 0.070 mmol) was dissolved in a mixed solution of THF (100 ml) and water (20 ml, buffered to pH 10.5 with 50 mmol dm^{-3} carbonate). To remove protecting groups this solution was treated with 2,2′-(methylimino)bisethanol (0.16 ml, 1.39 mmol) at room temperature for 8 h. Aqueous HCl (1.0 mol dm^{-3}) solution (20 ml) was added and the organic layer was separated. This solution was washed with saturated boric acid solution, 5% $NaHCO_3$ solution and water and dried over Na_2SO_4. After filtration, the filtrate was concentrated to dryness to give reddish purple powder: Yield 60%, mp (decomp) > 300 °C; ^{1}H NMR ($CDCl_3$; 27 °C) $\delta_H = -2.74$ (2H, s, NH of pyrrole), 6.53 (8H, s, OH), 7.70 (4H, t, ArH), 8.20 and 8.28 (8H, each d, ArH), 8.65 (4H, s, ArH), 8.81 (8H, s, CH of pyrrole). Found: C, 67.12; H, 4.40; N,

6.96%. Calcd for $C_{44}H_{34}B_4N_4O_8$: C, 66.90; H, 4.34; N, 7.09%.

5, 10, 15, 20-Tetrakis[3- or 4-(dihydroxyboryl)phenyl] Porphinatoiron(III) (1a or 1b). Compound **4a** (or **4b**: 20 mg, 0.070 mmol) and $FeCl_2$ (100 mg, 0.79 mmol) were dissolved in DMF (1 ml) and solution was heated at 60 °C for 120 h under a nitrogen atmosphere. The solution was diluted with aqueous 1 mol dm^{-3} HCl solution. The precipitate was corrected and subjected to the purification by column chromatography (silica gel, chloroform methanol = 30 : 1 v/v): Yield 56% for **1a** and 39% for **1b**, mp (decomp) > 300 °C. Found: C, 60.23; H, 3.40; N, 6.46% (**1a**) and C, 60.05; H, 3.47; N, 6.52% (**1b**). Calcd for $C_{44}H_{34}B_4N_4O_8FeCl$: C, 60.01; H, 3.67; N, 6.37%.

Miscellaneous. Column chromatography was performed on silica 60 (Merck 9385, 230—400 mesh). Melting points were determined on a Micro Melting Point Apparatus Yanaco MP-500D. UV-visible spectra, ^1H NMR spectra, IR spectra, CD spectra, and ESR spectra were recorded on a Shimadzu UV-160A spectrometer, Bruker AC-250P spectrometer, JASCO A-100 spectrometer, JASCO J-720 spectrometer and JEOL JES-FE1XG X-band spectrometer.

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