Highly Selective and Sensitive "Sugar Tweezer" Designed from a Boronic-Acid-Appended μ-Oxobis[porphinatoiron(III)]

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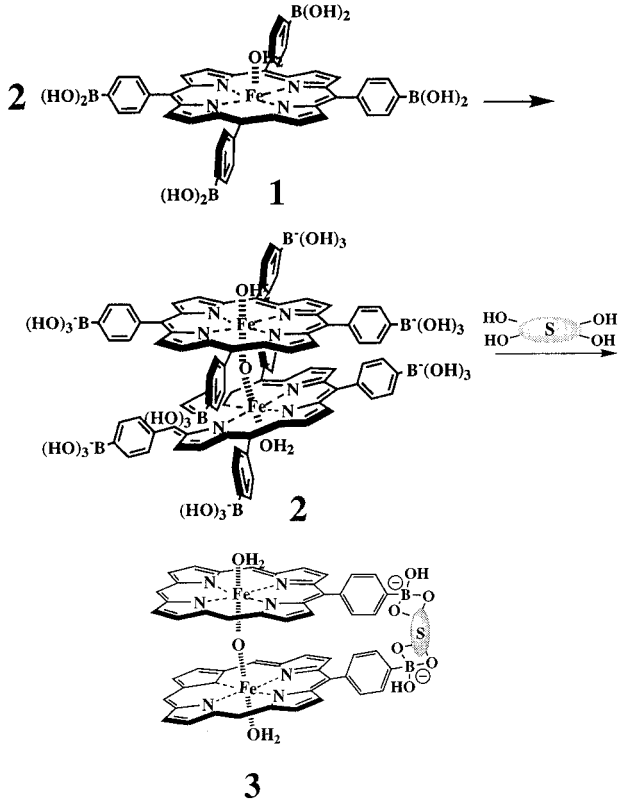
The development of artificial receptors which can precisely and specifically discriminate between guest molecules has become a very active area of endeavour. In most reported synthetic receptors, hydrogen-bonding interactions play a central role.[1] It is shown, however, that the hydrogen-bonding interactions are effective in aprotic solvents but less effective for recognition of guests (such as sugars) soluble only in aqueous solutions. The inefficient binding ability of such synthetic receptors prompted us to search for an alternative binding force useful in an aqueous system. Our group[2] as well as others[3−6] have thus started to exploit the interactions of boronic 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 saccharides in water by fluorescence and to predict the absolute configuration by circular dichroism (CD).[7,8] Through these studies it has become clear that one must manipulate two boronic acids in an appropriate spatial position to achieve successful two-point interrogation of a specific saccharide guest.[7,9] In these systems it is known that only when two boronic acids are intramolecularly bridged by a saccharide, resultant saccharide-containing macrocycles become CD-active.[2] 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: the μ-oxo dimer is formed stably in basic aqueous solution[10] where the boronic acid/saccharide complex is also formed stably.[2−7,9] Furthermore, the distance between two porphyrin planes (3.8 Å)[11] is comparable with the molecular size of monosaccharides (3.0 Å). We here report that **2** can selectively bind glucose and galactose (intramolecularly as in **3**, Scheme 1), among many monosaccharides, and their absolute configuration is readily determined from the sign of the CD spectra.

Scheme 1



The synthesis of compound **1** was reported previously.[7a,b] The iron(III) complex was synthesized according to the conventional method[10] and identified by elemental analysis. A plot of A_{418} (Soret band of **1** or **2**; measured at 25 °C, [**1**] = 1.00 × 10^{-5} M in MeOH/water = 1:300 v/v) vs pH was increased from pH 9.0 and saturated at pH 10.5 with ϵ_{418} = 77 000 M^{-1} cm^{-1}. The species formed at pH 10.5 gave a $\nu_{Fe-O-Fe}$ band at 850 cm^{-1} by IR spectroscopy.[12] These lines of spectral evidence support the view that **1** is converted to μ-oxo dimeric **2** at pH 10.5.

Examination of the absorption spectra of **2** at pH 10.5 in the absence and the presence of saccharides showed that they are scarcely affected by saccharide addition. In CD spectroscopy, only glucose and galactose could give the strong CD bands at Soret band region among many monosaccharides tested herein (Figure 1).[13] The CD intensity could be detected even for ~10^{-5} M glucose and galactose. Thus, one can conclude that ***2** acts as a highly selective and sensitive "sugar tweezer" for glucose and galactose*.

To obtain quantitative insights into the binding mode, we estimated the stoichiometry of the complexes by a continuous variation plot of CD intensity (θ_{obs} at 380nm) vs [**2**]/([**2**]+[D-glucose]) (Figure 2). A sharp maximum appeared at 0.5. D-Galactose also gave the maximum at 0.5. The results indicate that even though **2** has eight boronic acids, only two boronic acids are used to form the 1:1 **2**/saccharide complexes. Examination of CPK molecular models reveals that when two

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(13) Monosaccharides tested herein are glucose, galactose, mannose, arabinose, fructose, xylose, D-glucose-6-phosphate, and 1-*O*-methyl-α-D-glucoside.

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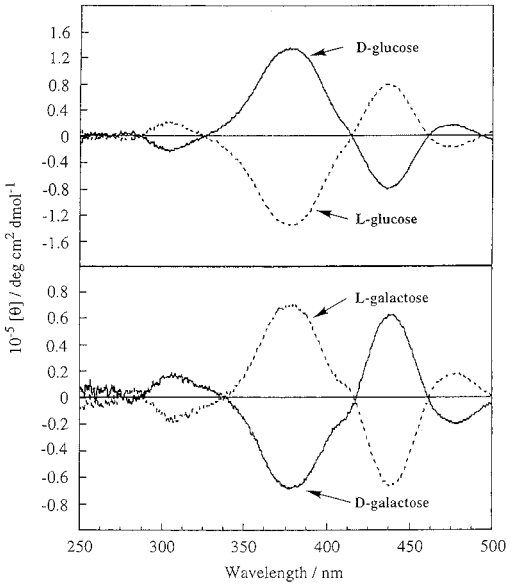

Figure 1. CD spectra of **2** (5.00×10^{-6} M) in the presence of D- or L-glucose (5.00×10^{-3} M) (A) and D- or L-galactose (5.00×10^{-3} M) (B): 25 °C, 0.3 vol% methanol, pH 10.5 with 0.05 M carbonate buffer.

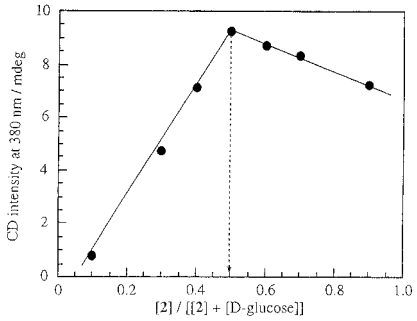

Figure 2. Continuous variation plot of CD spectra of **2** (5.00×10^{-6} to 4.50×10^{-5} M) in the presence of D-glucose (5.00×10^{-6} to 4.50×10^{-5} M): 25 °C, 0.3 vol% methanol, pH 10.5 with 0.05 M carbonate buffer.

boronic acids react with four OH groups in these saccharides, they must get close to each other and the Fe−O−Fe bond angle is deformed to 150° from the regular 180° bond angle. As a result, the distance between two boronic acids in remaining three pairs becomes too long to complex saccharides intramolecularly. Hence, this binding mode is classified into the negative allosterism. It is now clear that the origin of the CD activity is related to the chiral immobilization of two porphyrin rings in **2** by the "saccharide bridging". In fact, **2** in the presence of D-glucose-6-phosphate or 1-*O*-methyl-α-D-glucoside, which has only one boronic acid-binding site and therefore cannot bridge two porphyrin rings, was CD-silent. From plots of CD intensity (θ_{obs} at 380nm) vs [saccharide], we estimated the association constants (K_{assn}) to be 1.51×10^5 M^{-1} for glucose and 2.43×10^4 M^{-1} for galactose. *These values are the largest as artificial saccharide receptors and 1 to 2 orders of magnitude greater than those achieved so far.*[2,7] The results clearly indicate that μ-oxo dimers provide an excellent platform for designing boronic-acid-based saccharide receptors.

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 **2**·D-glucose complex (Figure 3). We chose D-mannose, D-allose, and D-galactose (epimers of D-glucose) as competing saccharides. D-Galactose, which has a K_{assn} 1/6 of that for D-glucose, affected the CD intensity even at the low D-galactose concentration. In

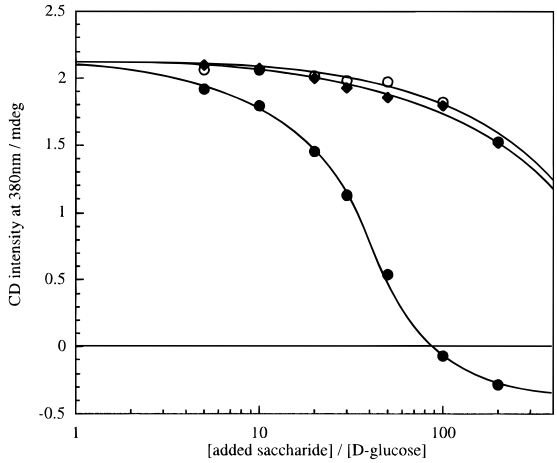

Figure 3. Semilogarithmic plots of the CD intensity for **2**·D-glucose complex against [added saccharide]/[D-glucose]: [**2**] = 5.00×10^{-6} M, [D-glucose] = 1.00×10^{-4} M, 25 °C, 0.3 vol% methanol, pH 10.5 with 0.05 M carbonate buffer; (●) D-galactose, (○) D-mannose, (♦) D-allose.

contrast, the CD intensity was scarcely affected by added D-mannose and D-allose up to [added saccharide]/[D-glucose] = 100. The results indicate that **2** possesses very high D-glucose selectivity and is useful as a D-glucose sensor even in the presence of these saccharides.

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 diboronic acids.[14] 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 acids in **2**, using 1,2-diol and 4,6-diol (in pyranose, 5,6-diol instead of 4,6-diol in furanose)[14]: 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 **2**. As shown in Figure 1, D- and L-isomers of these two saccharides show the symmetrical CD spectra. In addition, the CD spectrum of D-glucose is very similar to that of L-galactose. The sole difference in the absolute configuration between glucose and galactose is the direction of 4-OH. This implies that the absolute configuration of 4-OH controls the orientation of two porphyrins.

In conclusion, the present paper demonstrates that a highly selective and sensitive "sugar tweezer" can be designed utilizing an μ-oxobis[porphinatoiron(III)] as a basic platform and boronic acids as sugar-binding sites. The remarkably large association constants (10^4−10^5 M^{-1}) are comparable even with those of enzymes specific to these saccharides.[15] 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 onto the membrane system).

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