Meso–meso-linked porphyrin dimer as a novel scaffold for the selective binding of oligosaccharides†

Masato Ikeda,[a] Seiji Shinkai*[a] and Atsuhiro Osuka[b]

[a] *Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 812-8581, Japan. E-mail: seijitcm@mbox.nc.kyushu-u.ac.jp*

[b] *Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan*

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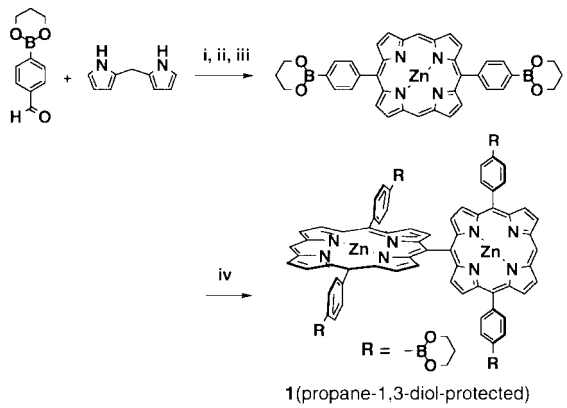
A meso–meso-linked porphyrin dimer 1 bearing four boronic acid groups shows high selectivity for maltotetraose (*n* = 4) among maltooligosaccharides (*n* = 1–7), indicating that this class of porphyrins acts as a novel scaffold to design oligosaccharide receptors.

The specific interaction between phenylboronic acids and saccharides or related compounds has been attracting increasing attention as a novel force for sugar recognition in aqueous systems.[1–8] Since one phenylboronic acid reacts with two OH groups to form a cyclic boronate ester, monosaccharides usually bearing five OH groups tend to form 1 : 2 monosaccharide–phenylboronic acid complexes.[1,9–13] However, the stability order of these complexes is always the same, which is governed by the inherent structure of monosaccharides.[2–4,14,15] Of such monosaccharides, fructose has a high association constant whereas glucose has a low association constant.[14,15] In contrast, diboronic acids which can react with four of the five OH groups to form intramolecular 1 : 1 complexes show a different stability order, which is related to the specific spatial position of two boronic acid groups. This implies that one can recognise a specific saccharide by appropriate manipulation of two boronic acids in the same molecule and the concept may be extended to the selective binding of oligosaccharides. This idea has been tested with a few diboronic acid systems bearing a 'long' spacer: *e.g.* diphenyl-3,3′-diboronic acid, stilbene-3,3′-diboronic acid and *cis*-5,15-bis[2-(dihydroxyboronyl)phenyl]-10,20-diphenylporphine show some selectivity for certain disaccharides but the selectivity observed so far is not very high.[16–18] We thus considered that one should look for a 'long' and 'rigid' scaffold by which one might finely tune the distance between two boronic acid groups. Recently, it was found that the meso–meso coupling reaction of Zn(II) porphyrinates is efficiently mediated by $AgPF_6$[19] to yield oligomeric porphyrins. These new compounds seem to satisfy the prerequisites mentioned above. As a preliminary step to use these compounds as scaffolds for saccharide recognition, we designed compound **1**. Very interestingly, we have found that **1** shows a high affinity with maltotetraose among maltooligosaccharides. To the best of our knowledge, this is the first artificial saccharide receptor which shows selectivity for oligosaccharides.

Compound **1** was synthesised from 4-(1,3-dioxaborinan-2-yl)benzaldehyde and dipyrrylmethane according to Scheme 1 and identified as its propane-1,3-diol-protected species by ^{1}H NMR and MALDI-TOF mass (*m/z* 1386.9) spectra and elemental analysis.‡ Since ^{1}H NMR spectroscopy showed that the protecting groups are readily eliminated in aqueous media to yield **1**, it was used for the spectroscopic measurements without deprotection treatment. From examination of Lambert–Beer plots, we found that **1** tends to aggregate in water-rich solvents. We thus chose a water (pH 10.5 with 50 mmol dm^{-3} carbonate buffer)–MeOH (2 : 3 v/v) mixture into which **1** was solubilised discretely.

† Electronic supplementary information (ESI) available (i) Fig. A and B (Job plot for **1**+M_4 and possible binding mode for **1**/M_4, respectively). See http://www.rsc.org/suppdata/cc/b0/b003365k/



Scheme 1 *Reagents and conditions* [yields]: i, TFA, CH_2Cl_2, r.t. then chloranil, reflux [30%]; ii, $Zn(OAc)_2$, $CHCl_3$–MeOH, r.t. [88%]; iii, propane-1,3-diol, benzene, reflux [98%]; iv, $AgPF_6$/MeCN, $CHCl_3$, r.t. [4%].

The absorption spectrum of **1** showed a split Soret band (412.0 and 448.0 nm) and a few Q bands (516.0, 560.0 and 594.5 nm). When maltooligosaccharides (M_n: α-1,4-linked oligomers of D-glucose) were added, the absorption spectra were scarcely changed, indicating that the skeleton of compound **1** is fairly rigid. In the circular dichrosim (CD) spectra, on the other hand, exciton-coupling-type CD bands appeared in the Soret band region (Fig. 1). It is seen from Fig. 1 that the CD spectra consist of two exciton-coupling bands: for the **1**·M_4 complex (Fig. 1), a negative band at higher wavelength and the positive band at shorter wavelength. The strongest peak appears at 417 nm where two CD bands overlap. The CD intensity at 417 nm is summarised in Table 1. It is seen from Table 1 that: (i) the complex with D-glucose (M_1) is almost CD-silent, (ii) maltose (M_2) and maltotriose (M_3) give a weak negative 417 nm peak whereas maltotetrose and higher-order maltooligosaccharides (M_5–M_7) all give a positive 417 nm peak and (iii) a particularly strong CD band is observed for M_4. The results indicate that (i)

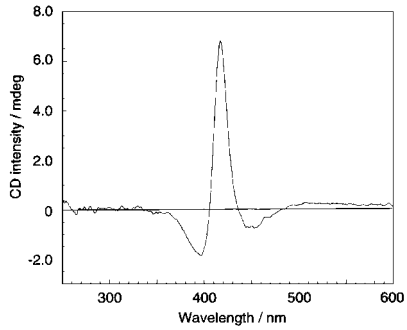


Fig. 1 CD spectrum of **1** (5.00×10^{-6} mol dm^{-3}) with a 1 cm cell in the presence of maltotetraose (50 mmol dm^{-3}) in a water (pH 10.5 with 50 mmol dm^{-3} carbonate)–MeOH (2 : 3) mixture at 25 °C. A similar CD spectral shape was also observed (although the intensity was different) in the presence of other maltooligosaccharides.

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Table 1 CD intensity at 417 nm and binding parameters obtained from Hill's plots and substitution methods

Saccharide	CD intensity[a]/ mdeg	K^b/dm^6 mol^{-2}	m^b	K^c/dm^6 mol^{-2}
Glucose (M_1)	0.2	—	—	2.5×10^3
Maltose (M_2)	−0.5	—	—	1.5×10^3
Maltotriose (M_3)	−0.2	—	—	2.0×10^3
Maltotetraose (M_4)	6.8	6.3×10^5	1.7	—
Maltopentaose (M_5)	1.9	1.3×10^4	1.8	—
Maltohexaose (M_6)	1.4	1.6×10^4	1.8	—
Maltoheptaose (M_7)	1.7	2.0×10^3	1.5	—

[a] See caption of Fig. 1. [b] Determined from Hill's plots. [c] The 1:2 to 1:2 substitution (*e.g.* from **1**·$(M_4)_2$ to **1**·$(M_1)_2$) is assumed for the calculation.

D-glucose is too small to bridge two boronic acid groups, (ii) the two porphyrin planes are oriented in opposite directions for the M_2, M_3 complexes and M_4–M_7 complexes, respectively, and (iii) M_4 forms a particularly stable complex with **1**.

To obtain further insights into the binding mode, the complex stoichiometries were estimated by a Job plot method for M_4–M_7 which show measurable CD intensity. A typical example for M_4 is shown in Fig. A(ESI):† a maximum is observed at ([**1**]/([**1**] + [M_4]) = 0.33. This supports the view that **1** binds two M_4 guests to form the stable complex. Similar 1:2 stoichiometries were also observed for M_5, M_6 and M_7. The computational studies (Discover 3/Insight II 98.0) predict that in the most stable conformation the two porphyrin planes cross at 90°, in which the distance between two boron atoms is 1.58 nm. This distance is comparable with that between the 1,2-diol and 4,6-diol in the two terminal D-glucose units of M_4 (*ca.* 1.5–1.8 nm). One may thus illustrate a binding mode for the 1:2 **1**/M_4 complex as shown in Fig. B(ESI).†§

The CD spectra measured as a function of M_4–M_7 concentrations provided several isosbestic points. As typical examples, plots of CD intensity at 417 nm *vs.* [M_4] and [M_5] are shown in Fig. 2. The sigmoidal curvatures indicate that the 1:2 complexes are formed in a cooperative manner. Similar sigmoidal dependences were also observed for M_6 and M_7. The binding of the guest to **1** is cooperative. This cooperative guest binding profile can be analysed with the Hill equation: $\log [y/(1 - y)] = m\log[\text{guest}] + \log K$, where K and m are the association constant and Hill coefficient, respectively, and $y = K/([\text{guest}]^{-m} + K)$.[20] From the slope and the intercept obtained using the linear portion at $\log [y/(1 - y)] = 0$–0.8 we obtained K and m values for M_4–M_7. The determination of K values for M_1–M_3 was difficult because of their weak CD intensity, but measurements were obtained by a substitution method using the **1**·M_4 complex, that is, by the CD intensity decrease induced by addition of M_1–M_3, and the results are summarised in Table 1. Examination of Table 1 reveals that: (i) the magnitude of K is correlated with the CD intensity, (ii) the largest K is observed for M_4, which is 48- and 39-fold larger, respectively, than those of M_5 and M_6 and (iii) the m values are smaller than 2.0, indicating the weak positive allosterism and the presence of the 1:1 species in the low saccharide concentration region. This novel binding mode implies that the binding of the first guest which intramolecularly bridges two boronic acid groups suppresses the rotational freedom of the porphyrin rings and preorganises the two residual boronic acids so that they can easily complex the second guest.

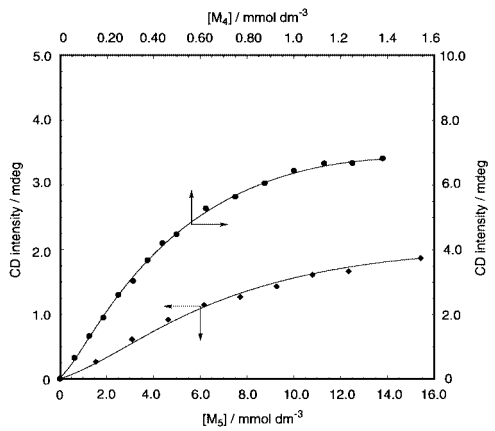

Fig. 2 Plots of CD intensity (417 nm) for **1** (5.00×10^{-6} mol dm^{-3}) *vs.* [M_4] and [M_5].

In conclusion, it was shown that the meso–meso-linked porphyrin dimer is a useful scaffold to separate two boronic acid groups so that they can show selectivity for oligosaccharides. We believe that this study is very important in revealing boronic acid–saccharide interactions toward selective recognition of oligosaccharides.

Notes and references

‡ In step iv (Scheme 1), by-products were detected in which the boronic acid groups were substituted by OH groups. The raw yield of **1** estimated by HPLC was *ca.* 20%.

§ Conformations with low potential energy encountered during a 100 ps MD simulation at 300 K were selected. The system was minimised using conjugate gradient and Newton–Raphson methods until convergence was attained for a gradient of 0.01 kcal mol^{-1} Å^{-1}. The force field used in this study was the ESFF.

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