Sugar-induced Chiral Orientation of a Boronic-acid-appended Porphyrin Stack. Correlation between the Absolute Configuration and the CD (Circular Dichroism) Sign

Tomoyuki Imada, Hiroto Murakami and Seiji Shinkai*

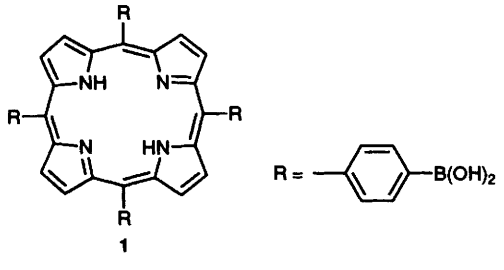
Department of Chemical Science & Technology, Faculty of Engineering, Kyushu University Hakozaki, Fukuoka 812, Japan

A boronic-acid-appended porphyrin (**1**) forms stacked aggregates in aqueous solution and in the presence of sugars the aggregates give exciton-coupling bands specific to the absolute configuration of added sugars.

The development of artificial receptors which can precisely and specifically discriminate between guest molecules has become a very active area of endeavour.[1] We have recently been interested in the development of new sugar recognition methods useful in an aqueous system.[2–6] Here, we came across an interesting paper reported by Fuhrhop *et al.*[7]: protoporphyrins covalently-linked to glucosamine form fibrous aggregates with a chiral helical structure. The results suggest that aggregates formed from boronic-acid-appended porphyrins may be orientated in a chiral manner in the presence of sugars. As a result, the absolute configuration of added sugars may be '*read out*' through the sign of the CD (circular dichroism) spectra. With these objects in mind we synthesized a boronic-acid-appended porphyrin (**1**).

Compound **1** was synthesized from pyrrole and 1,3-dioxa-2-(4-formylphenyl)-5,5-dimethylborinane in dichloromethane in the presence of trifluoroacetic acid according to the method of Lindsey *et al.*[8] Deprotection of the 5,5-dimethylborinane rings by treatment with tetramethylammonium hydroxide gave **1**: yield 4%, mp (decomp.) > 300 °C. The product was identified by IR and ^{1}H NMR spectroscopic evidence and elemental analysis.

Firstly, we confirmed by spectroscopic methods if **1** aggregates in aqueous solution. Compound **1** gave a sharp Soret band in DMSO (λ_{max} 427 nm) and in water–DMSO (30 : 1 v/v) at pH 10.5 (λ_{max} 421 nm) but a broadened Soret band in water–DMSO (30 : 1 v/v) at pH 6.9 (λ_{max} 321 nm). The pK_a of boronic acids is estimated to be *ca.* 8.9 by a photometric titration. Hence, the spectral data reveal that **1** exists discretely when the boronic acids are dissociated whereas it forms aggregates when the boronic acids are undissociated. This difference was further corroborated by fluorescence spectroscopy. Although the strong fluorescence emission (λ_{EX} 433 nm, λ_{EM} 657 nm) was observable at pH 10.5, it almost disappeared at pH 6.9. The difference can be accounted for by a pH-dependent shift of an aggregation-deaggregation equilibrium in **1**. When D-arabinose, D-galactose or D-mannose was added to a solution of **1** at pH 6.9, the fluorescence intensity increased only slightly. On the other hand, a relatively large increase was observed when D-fructose was added. The fluorescence intensity increased in the order D-fructose ≫ D-arabinose > D-galactose > D-mannose > D-glucose. Since this order is in line with the order of the association constants between phenylboronic acid and monosaccharides,[9,10] one can consider that complexation of the boronic acids with monosaccharides makes **1** more hydrophilic and induces partial dissociation of the aggregates.



1

The main purpose of the present study is to *read out* the absolute configuration of monosaccharides through the sign of the exciton-coupling band (ECB). The appearance of ECB is expected when **1** aggregates in solution because the exciton-coupling is a phenomenon related to the dipole–dipole interaction in the excited state. To suppress the monosaccharide-induced deaggregation we carried out the CD spectral measurement at [**1**] = 1.00 mmol dm^{-3} (for the measurement conditions see Table 1). When D-fructose (0.50 mol dm^{-3}) was added, the solution of **1** was almost CD-silent. On the other hand, when other monosaccharides (0.50 mol dm^{-3}) listed in Table 1 were added, it became CD-active. The spectral parameters are summarized in Table 1. Typical examples are shown in Fig. 1. The solvent composition was chosen so that the exciton-coupling bands can appear distinctly. In general, monosaccharides with large association constants required low DMSO concentrations.

When boronic acids form complexes with monosaccharides, the binding-site is selected according to several rules.[2–5] Firstly, when they form a five-membered ring with 1,2- or 3,4-diols, the *cis*-configuration is favoured. Secondly, when they form a six-membered ring with a 4,6-diol, both *cis* and *trans* complexes can form. However, the spatial position of Ar in $ArB(OH)_2$ is governed by the configuration of 4-OH. Thirdly, the effective configuration of 1-OH for complexation is *cis* to 2-OH. Based on these rules one can summarize the possible binding-sites in monosaccharides as in Table 1, where 'up' and 'down' denote that the OH groups are placed upwards and

Table 1 CD spectral parameters[a]

Monosaccharide	Medium[b]	λ_{max} or λ_{min} (nm) ([θ]/° cm^2 dmol^{-1})			Configuration of binding-sites		
					1,2[c]	3,4	4,6[d]
D-Xylose	A	433 (+1.8 × 10^4)	414 (−1.6 × 10^4)		Down/*cis*	—	—
Methyl-α-D-glucoside	A	433 (+5.6 × 10^3)	417 (−3.6 × 10^3)		—	—	Down/*trans*
D-Glucose	A	430 (+1.7 × 10^4)	414 (−2.1 × 10^4)		Down/*cis*	—	Down/*trans*
D-Talose	B	436 (−1.5 × 10^4)	420 (+3.8 × 10^4)	402 (−1.6 × 10^4)	Up/*cis*	Up/*cis*	Up/*cis*
D-Galactose	B	439 (−3.7 × 10^4)	420 (+3.1 × 10^4)	399 (−5.0 × 10^3)	Down/*cis*	Up/*cis*	Up/*cis*
D-Mannose	B	425 (−3.8 × 10^3)	412 (+3.2 × 10^3)		Up/*cis*	—	Down/*trans*
D-Ribose	A	443 (+1.5 × 10^4)	432 (−2.8 × 10^4)	417 (+2.9 × 10^4)	Down/*cis*	Down/*cis*	—
D-Arabinose	B	435 (−2.2 × 10^3)	422 (+3.2 × 10^3)	415 (+1.4 × 10^3)	Up/*cis*	Down/*cis*	—

[a] [**1**] = 1.00 × 10^{-3} mol dm^{-3}, [monosaccharide] = 0.50 mol dm^{-3}, 25 °C. [b] A, water–DMSO (5 : 2 v/v) B, water–DMSO (6 : 1 v/v). The water used for the preparation of mixed solvents is buffered to pH 6.9 with 0.10 mol dm^{-3} phosphate. [c] 'Up' or 'down' is governed by the direction of 2-OH. [d] 'Up' or 'down' is governed by the direction of 4-OH.

downwards, respectively, relative to the pyranose ring. In D-xylose the sole binding-site is *cis*-1,2-diol and the **1**·D-xylose complex results in a positive ECB with the positive first Cotton effect and the negative second Cotton effect. In methyl-α-D-glucoside the sole binding site is *trans*-4,6-diol and the **1**·methyl-α-D-glucoside complex results in a positive ECB. The CD spectrum for the **1**·D-xylose complex is stronger than that for the **1**·methyl-α-D-glucoside complex. The findings suggest that (*i*) when 'down'-*cis*-1,2-diol or 'down'-*trans*-4,6-diol is bound to **1**, the dipoles of **1** in the aggregate cross in the (*R*)-chirality (clockwise direction), (*ii*) as 'down'-*cis*-1,2-diol and 'down'-*trans*-4,6-diol give a positive ECB, it is expected that enantiomeric 'up'-*cis*-1,2-diol and 'up'-*cis*-4,6-diol give a negative ECB and (*iii*) when 1,2-diol and 4,6-diol give the opposite CD sign, the CD sign for 1,2-diol dominates over that for 4,6-diol but the CD intensity is weakened. From these considerations, it is readily understandable that D-glucose with 'down'-*cis*-1,2-diol and 'down'-*trans*-4,6-diol as the binding-sites gives a strong positive ECB. On the other hand, D-mannose has 'up'-*cis*-1,2-diol giving a negative ECB and 'down'-*trans*-4,6-diol giving a positive ECB. As pointed out in (*iii*), the former predominates over the latter. In fact, the **1**·D-mannose complex gives rise to a weak negative ECB. The rules can be extended to other monosaccharides: a strong negative ECB for D-talose with 'up'-*cis*-1,2-diol and 'up'-*trans*-4,6-diol, a positive ECB for D-ribose with 'down'-*cis*-1,2-diol and a negative ECB for D-arabinose with 'up'-*cis*-1,2-diol. One exception is D-galactose: from the above-mentioned rules it should give a weak positive ECB but actually, a weak negative ECB was observed.†

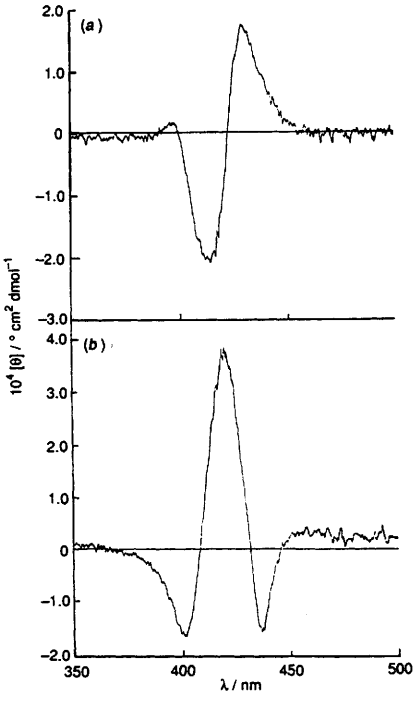


Fig. 1 CD spectra of **1** (1.00×10^{-3} mol dm^{-3}) at 25 °C and pH 6.9 with 0.10 mol dm^{-3} phosphate buffer: (*a*) [D-glucose] = 0.50 mol dm^{-3}, water–DMSO (5:2 v/v); (*b*) [D-talose] = 0.50 mol dm^{-3}, water–DMSO (6:1 v/v). L-Isomers afforded the CD spectra symmetrical to those illustrated above.

Table 2 Correlations between the absolute configuration of monosaccharides and the sign of exciton-coupling bands

Configuration		Sign of exciton-coupling at 420–440 nm	Configuration	Sign of exciton-coupling at 400–420 nm
cis-1,2-Diol	*cis*/*trans*-4,6-Diol		*cis*-3,4-Diol	
Down	—	Positive	Up	Positive
—	Down	Positive	Down	Negative
Up	—	Negative		
(—	Up)	(Negative)[a]		
Down	Down	Positive		
Up	Up	Negative		
Up	Down	Negative		
Down	Up	(?)[b]		

[a] It is surmised that this configuration gives a negative ECB but we could not procure the sample. [b] We expected that this configuration gives a positive ECB but D-galactose gave a weak negative ECB.

D-Talose, D-galactose, D-ribose and D-arabinose gave a second ECB at shorter wavelengths. This ECB was observed only for such monosaccharides that possess *cis*-3,4-diol. Therefore, it seems reasonable to assign this band to complexation between **1** and the 3,4-diol. Here again, one can recognize a correlation between the configuration and the CD sign: D-talose and D-galactose with 'up'-*cis*-3,4-diol give a positive ECB whereas D-ribose and D-arabinose with 'down'-*cis*-3,4-diol give a negative ECB.

In conclusion the present study demonstrated that the absolute configuration of monosaccharides is predictable by a CD spectroscopic method: the correlations between the absolute configuration and the CD sign are summarized in Table 2. The idea is ultimately related to the sugar-binding ability of boronic acids appended to a porphyrin which induces a chiral orientation of porphyrin stacks. The results argue that boronic acids serve as a useful sugar-interface to recognize sugars and *read out* their absolute configuration.

Received, 1st February 1994; Com. 4/00639I

Footnote

† In the CD studies of monosaccharides D-galactose frequently shows exceptional behaviour.[2] The reason is not well understood. In this paper the discussions were made on pyranose forms but similar discussions are possible in furanose forms.

References

1 For comprehensive reviews, see J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 245 and A. D. Hamilton, *Bioorg. Chem. Front.*, 1991, **2**, 115.
2 K. Tsukagoshi and S. Shinkai, *J. Org. Chem.*, 1991, **56**, 4089; Y. Shiomi, M. Saisho, K. Tsukagoshi and S. Shinkai, *J. Chem. Soc., Perkin Trans. 1*, 1993, 211.
3 K. Kondo, Y. Shiomi, M. Saisho, T. Harada and S. Shinkai, *Tetrahedron*, 1992, **48**, 8239; Y. Shiomi, K. Kondo, M. Saisho, T. Harada, K. Tsukagoshi and S. Shinkai, *Supramol. Chem.*, 1993, **2**, 11.
4 S. Shinkai, K. Tsukagoshi, Y. Ishikawa and T. Kunitake, *J. Chem. Soc., Chem. Commun.*, 1991, 1039; R. Ludwig, K. Ariga and S. Shinkai, *Chem. Lett.*, 1993, 1413.
5 T. D. James, T. Harada and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1993, 857, 1176 (Corrigendum).
6 The similar idea to use the boronic acid as a sugar interface was reported recently: J. Yoon and A. W. Czernik, *J. Am. Chem. Soc.*, 1992, **114**, 5874 and M.-F. Paugan and B. D. Smith, *Tetrahedron Lett.*, 1993, **34**, 3723.
7 J.-H. Fuhrhop, C. Demoulin, C. Boettcher, J. Könnig and U. Siggel, *J. Am. Chem. Soc.*, 1992, **114**, 4159.
8 J. S. Lindsey, I. C. Schreiman, H. C. Hsw, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.
9 H. Murakami, T. Nagasaki, I. Hamachi and S. Shinkai, *Tetrahedron Lett.*, 1993, **34**, 6273.
10 A. Otsuka, T. Nagata, F. Kobayashi and K. Maruyama, *J. Heterocycl. Chem.*, 1990, **27**, 1657.