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Sugar-Assisted Chirality Control of Tris(2,2'-bipyridine)-Metal Complexes

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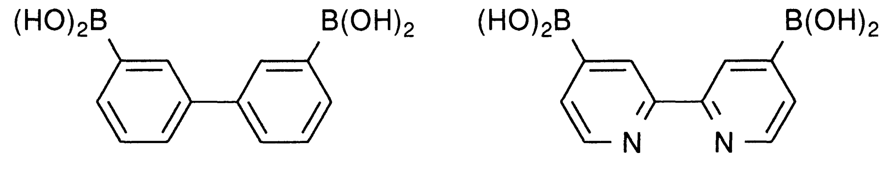
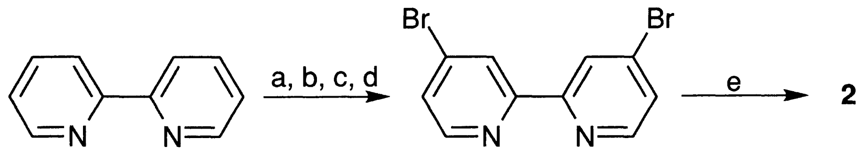
2,2'-Bipyridine-4,4'-diboronic acid (**2**), a 2,2'-bipyridine derivative with sugar-binding sites was synthesized. The Δ *vs.* Λ chirality of the $Fe^{2+}\cdot\mathbf{2}_3$ complex was selectively generated in correlation with the absolute configuration of added saccharides.

Boronic acids, which have been known since a long time ago to form covalently-bonded complexes with diols in an aqueous system, now attract a great deal of attention as a new interactive tool for sugar recognition.[1-8] We previously designed compound **1** to recognize disaccharides: the distance between two boronic acids in **1** with a syn conformation is *ca.* 7.4 Å, which is comparable with the distance between 1,2-diols and 4',6'-diols in disaccharides (assuming a linear conformation) serving as boronic-acid-binding sites.[5] Interestingly, only when **1** formed cyclic 1:1 complexes with disaccharides (*e.g.*, D-maltose, D-cellobiose, and D-lactose), clear exciton coupling bands appeared in circular dichroism (CD) spectroscopy because of asymmetric immobilization of the two benzene rings.[5] We considered that this concept could be further extended to the generation of novel sugar-assisted asymmetry, for example, Δ *vs.* Λ metal complexes by using **2** as a metal ligand: that is, the chirality generated in **2** through the complexation with disaccharides would be eventually reflected as the Δ *vs.* Λ enantioselectivity in the metal·$\mathbf{2}_3$ complex. To test the feasibility of this idea we synthesized **2** according to Scheme 1[9] and estimated the chirality of the Fe^{2+} complexes in the presence of saccharides by CD spectroscopy.[10]



1 **2**



Conditions: a) H_2O_2/CH_3COOH b) fuming HNO_3/fuming H_2SO_4 c) CH_3COBr/CH_3COOH d) $PBr_3/CHCl_3$ e) (i) *n*-BuLi/THF, -90 °C (ii) B(O*i*Pr)$_3$/THF, -90 °C (iii) H_2O

Scheme 1.

Compound **2** was identified by IR, ^{1}H NMR, and mass spectral evidence.[11] Figure 1 shows the CD spectra of **2** in the presence of D-maltose ($[\theta]_{205}$ = -2900 deg cm^2 dmol^{-1}) or D-cellobiose ($[\theta]_{212}$ = 6600 deg cm^2 dmol^{-1}). It is known that **1** shows the negative exciton coupling with the negative first Cotton effect and the positive second Cotton effect in the presence of D-maltose and the positive exciton coupling with the positive first Cotton effect and the negative second Cotton effect in the presence of D-cellobiose.[5] The coincidence between the CD sign in Fig. 1 and that of the first Cotton effect in the disaccharide·**1** complexes suggests that the bands in Fig. 1 correspond to the first Cotton effect in the exciton coupling.

A plot of $[\theta]_{205}$ against D-maltose concentration is shown in Fig. 2. The concentration dependence is biphasic with a $[\theta]_{205}$ minimum. Other disaccharides also showed a similar dependence. A similar concentration dependence was previously observed for **1**.[5] This is rationalized by the successive complex formation from a CD active cyclic 1:1 complex at the low disaccharide concentration to a CD-silent noncyclic 1:2 **1** (or **2**) / disaccharide complex at the high disaccharide concentration (Scheme 2).[12]

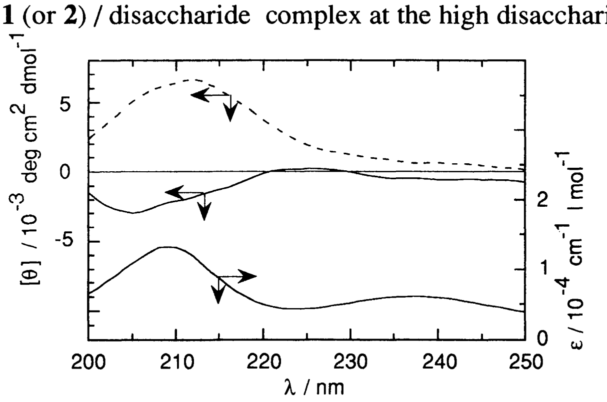


Fig. 1. CD spectra of **2** (5.0 mM) in the presence of D-maltose (50 mM, ——) or D-cellobiose (50 mM, - - - - -) and absorption spectrum of **2** (32.4 mM): 25 °C, pH = 10.5.

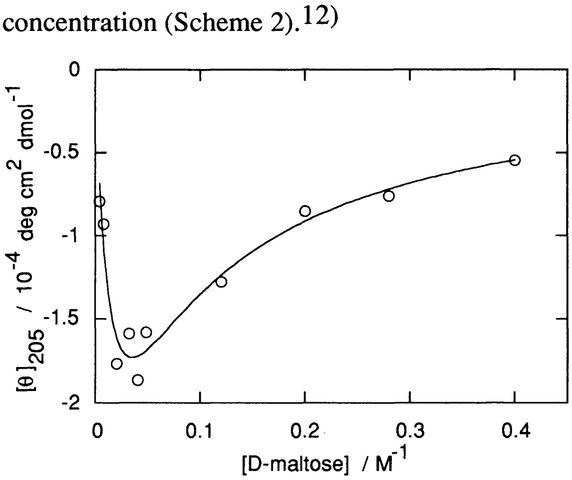
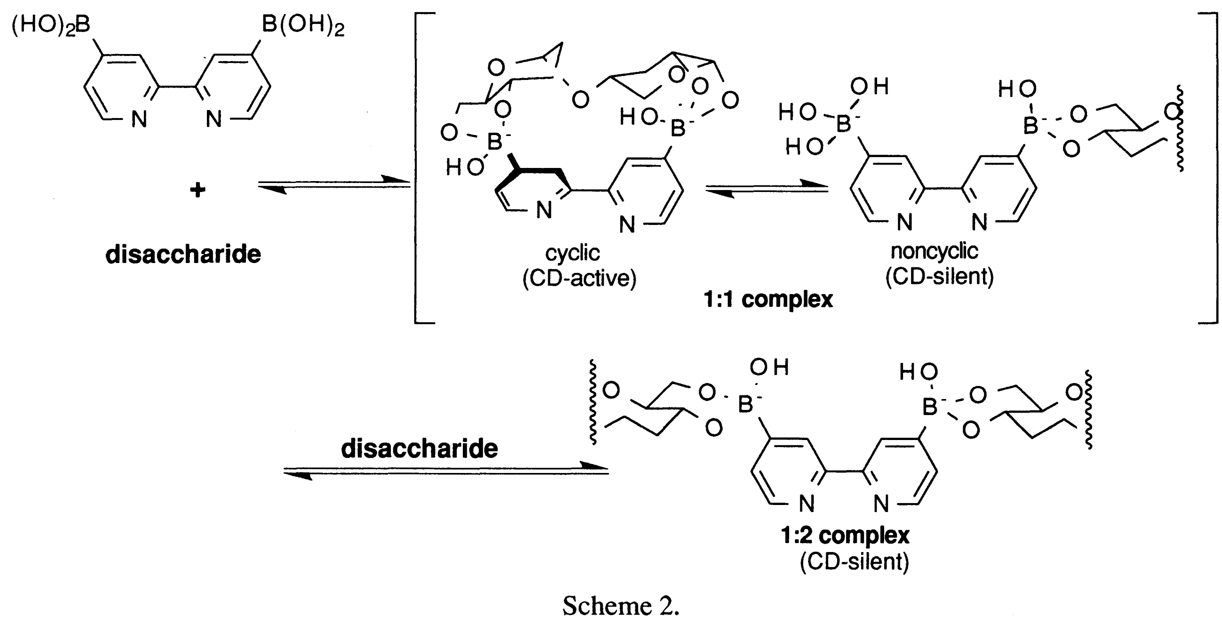


Fig. 2. Plot of $[\theta]_{205}$ *vs.* [D-maltose]: 25 °C, pH = 10.5, [**2**] = 5.0 mM.



Scheme 2.

Very interestingly, we found that when Fe^{2+} (added as $FeCl_2$) is added to the solution containing the disaccharide·**2** complex, the CD spectrum with an exciton coupling band appears at the metal-ligand charge-transfer (MLCT) band region (Fig. 3). The same CD spectrum was produced when disaccharide was added to the solution containing the Fe^{2+}·**2**$_3$ complex. Separately, we confirmed that the $[Fe(2,2\text{-bipyridine})_3]^{2+}$ is CD silent even in the presence of disaccharides. Hence, the CD-activity is attributable to the generation of chiral Fe^{2+} complexes which is originated from the disaccharide-diboronic acid interaction. Figure 3 shows that Fe^{2+}·(**2**·D-maltose)$_3$ adopts Λ chirality while Fe^{2+}·(**2**·D-cellobiose)$_3$ adopts Δ chirality.[13)]

Figure 4 shows a plot of $[\theta]_{556}$ ([θ] minimum) and $[\theta]_{480}$ ([θ] maximum) at the MLCT band region *vs*. D-maltose concentration. Strangely, the MLCT band region is still CD active in the presence of excess D-maltose while **2** itself becomes CD-silent.[5)] This implies that in **2** the intramolecular cross-link of two boronic acids is indispensable to the CD-activity whereas in Fe^{2+}·(**2**·disaccharide)$_3$ it is not a prerequisite to the CD-activity. This was further corroborated by the CD-activity observed in the presence of D-glucose 1-phosphate ($[\theta]_{543}$ = -1000, $[\theta]_{512}$ = 0, and $[\theta]_{480}$ = 540 deg cm^2 $dmol^{-1}$), D-glucose 6-phosphate ($[\theta]_{561}$ = 1600, $[\theta]_{524}$ = 0, and $[\theta]_{486}$ = -870 deg cm^2 $dmol^{-1}$), and α-methyl D-glucopyranoside ($[\theta]_{563}$ = -2700, $[\theta]_{522}$ = 0, and $[\theta]_{481}$ = 1700 deg cm^2 $dmol^{-1}$) which have only one boronic-acid-binding site and cannot cross-link two boronic acids intramolecularly (Fig. 5). The results indicate that the Δ $\rightleftharpoons$ Λ interconversion can take place even 4 °C and the CD sign for the thermodynamically more stable enantiomer appears.

At present we cannot yet determine the optical purity of the Fe^{2+}·(**2**·disaccharide)$_3$ complexes because the effort toward the optical resolution (we have tried the resolution by chiral-packed columns, diastereomer formation with tartaric acid, *etc.*) is unsuccessful so far.

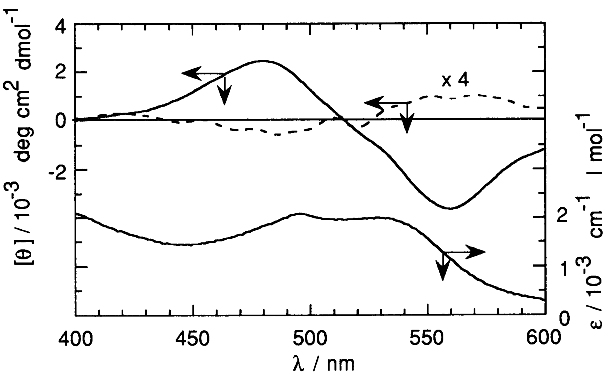


Fig. 3. CD spectra of Fe^{2+}·**2**$_3$ (6.0 mM) in the presence of D-maltose (18 mM, ———) and D-cellobiose (18 mM, - - - - -): 4 °C, pH = 10.5 and absorption spectrum of Fe^{2+}·**2**$_3$ (0.5 mM): 25 °C, pH = 10.5.

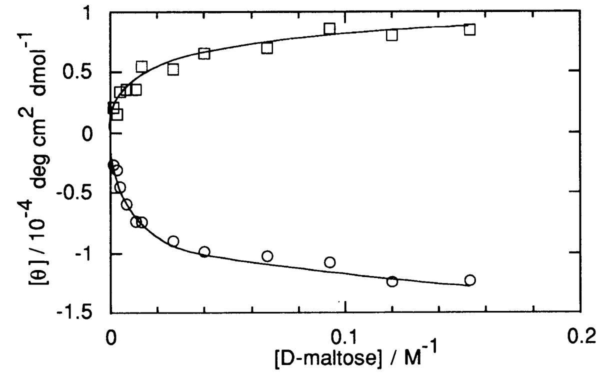


Fig. 4. Plot of $[\theta]_{556}$ (O) and $[\theta]_{480}$ (□) *vs*. [D-maltose]: 25 °C, pH = 10.5, [Fe^{2+}·**2**$_3$] = 6.0 mM.

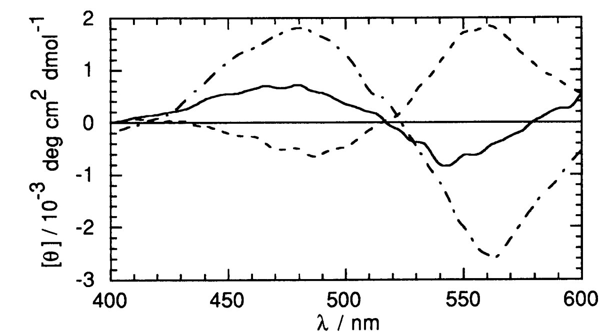


Fig. 5. CD spectra of [Fe^{2+}·**2**$_3$] (6.0 mM) in the presence of D-glucose 1-phosphate (added as dipotassium salt, 600 mM, ———), D-glucose 6-phosphate (added as potassium salt, 600 mM, - - - - -), and α-methyl D-glucopyranoside (600 mM, —·—·): 4 °C, pH = 10.5.

Judging from the [θ] value determined for optically-pure $[Fe(2,2'\text{-bipyridine})_3]^{2+}$,[13] we presume that the optical purity of $Fe^{2+}\cdot(\mathbf{2}\cdot\text{D-maltose})_3$ which gives the largest [θ] value in the present system is *ca.* 20%.

In conclusion, the present study has demonstrated that the Δ *vs.* Λ chirality of the $Fe^{2+}\cdot\mathbf{2}_3$ complex can be selectively generated by the saccharide addition and the selectivity is correlated with the absolute configuration of added saccharides. This is a novel application of a boronic-acid-dependent sugar-interface to the chirality control of metal complexes.

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9) 4,4'-Dibromo-2,2'-bipyridine was synthesized according to the following papers: J. Haginiwa, *Yakugaku Zasshi*, **75**, 731 (1955); G. Maerker and F. H. Case, *J. Am. Chem. Soc.*, **80**, 2745 (1958); D. Wenkert and R. B. Woodward, *J. Org. Chem.*, **48**, 283 (1983). However, we modified the reaction conditions to attain the higher yields: see a caption to Scheme 1.
10) Fe^{2+} was chosen to make the system simple because $[Fe(bpy)_3]^{2+}$ is formed in preference to $[Febpy]^{2+}$ and $[Fe(bpy)_2]^{2+}$; see M. R. McWhinnie and J. D. Miller, *Adv. Inorg. Chem. Radiochem.*, **12**, 135 (1969).
11) Compound **2** was obtained as white powder; mp 463 °C (dec.); IR (KBr) 3450 cm^{-1} (OH); ^1H NMR (CD_3OD) δ = 7.56 (2H, dd, H_5 and $H_{5'}$), 8.17 (2H, s, broad, H_3 and $H_{3'}$), 8.37 (2H, dd, H_6 and $H_{6'}$), $J_{3,5} = J_{3',5'} = 1.0$ Hz, $J_{3,6} = J_{3',6'} = 1.0$ Hz, $J_{5,6} = J_{5',6'} = 4.9$ Hz; MS (SIMS(-)) *m/z* 243 ($(M-1)^-$).
12) UV absorption spectra of **2** were scarcely affected by the addition of saccharides. So, we think that there is no big difference in the dihedral angle between free **2** and 1:1 **2**·disaccharide complex. Thus, the CD spectra should arise from the shift of the equilibrium between (R)- and (S)-atropisomers.
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