A boronic acid–diol interaction is useful for chiroselective transcription of the sugar structure to the Δ- *versus* Λ-$[Co^{III}(bpy)_3]^{3+}$ ratio

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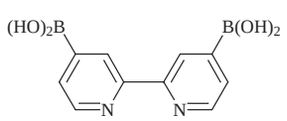
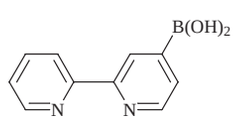
In order to apply boronic acid–saccharide interactions to the chiroselective synthesis of Δ- and Λ-$[Co^{III}(bpy)_3]^{3+}$ saccharide-binding ligands, 2,2′-bipyridine-4-boronic acid (bpymb) and 2,2′-bipyridine-4,4′-diboronic acid (bpydb) were newly synthesized. It was shown that most D-saccharides form cyclic 1 : 1 complexes with bpydb to afford the CD-active species. The positive exciton coupling band implies that two pyridine rings are twisted in a clockwise direction ((*R*)-chirality). In contrast, such a CD-active species was not yielded from bpymb. The treatment of the bpydb–D-saccharide complexes with $Co(OAc)_2$ gave the substitution-active $[Co^{II}(bpyba)_3]^{4-}$–saccharide complexes, which were oxidized to the substitution-inactive $[Co^{III}(bpyba)_3]^{3-}$–saccharide complexes. In this stage, the Δ *vs.* Λ ratio was fixed. The complexes were converted to $[Co^{III}(bpy)]^{3+}$ by treatment with $AgNO_3$ and the e.e. was determined by comparison with authentic Δ- or Λ-$[Co^{III}(bpy)]^{3+}$. The Δ-isomer was obtained in excess from most D-saccharides but the Λ-isomer was also obtained from D-fructose and D-fucose. At 4 °C, the largest e.e. for bpydb was attained with D-glucose (47% e.e.; Δ excess). Under the same reaction conditions the bpymb + D-glucose system gave 16% e.e. (Δ excess). The e.e. of the bpydb + D-glucose system increased with lowering the reaction temperature and at −25 °C it reached 79% e.e. The foregoing results clearly establish that the saccharide-templated synthesis is useful as a new concept for the preparation of chiral tris(2,2′-bipyridine)–metal complexes. Furthermore, the Δ *vs.* Λ equilibrium can be shifted in either direction by the selection of saccharide enantiomers.

Introduction

Saccharides are abundant chiral resources that Nature presents us. However, the chemistry utilizing saccharides as chiral building-blocks or chiral auxiliaries has not yet been sufficiently exploited. This is due to the difficulty or the lack of methodology to transcribe the chirality information stored in saccharides into desired molecules or molecular assemblies. Since the chemistry of saccharides plays a very important role in the metabolic pathways of living organisms, the detection of biologically important saccharides is necessary in a variety of medical, diagnostic and industrial contexts. Then, how can we '*touch*' saccharides which have been '*untouchable*' with an artificial receptor, particularly, when they are dissolved in aqueous solution? Although hydrogen-bonding interactions play a central role in most reported artificial receptors,[1] it has recently been shown that boronic acid–diol covalent interactions which readily and reversibly form in aqueous media represent an important alternative binding force in the recognition of saccharides and related molecular species.[2–7] Stable boronic acid-based saccharide receptors offer the possibility of designing saccharide sensors which are selective and sensitive for a specific saccharide.[6] Of particular interest are fluorescent saccharide sensors in which the photoinduced electron-transfer (PET) mechanism is integrated within a molecule.[8] Through these studies we have noticed that boronic acid–saccharide interactions create a variety of supramolecular structures which are founded on the absolute configuration of each saccharide.[9–11] This implies that saccharides are very useful as chiral building-blocks to create oriented supramolecular assemblies or as chiral auxiliaries for asymmetric syntheses. This viewpoint has escaped attention for a long time, even though Nature gives us a variety of saccharides with chiral structures. The object of the present study is to exploit a new cascade-type transmission system for (i) reading-out of the '*structural information*' stored in the saccharide configuration, (ii) chiroselective transcription into other vehicles and (iii) immobilization as a new information source. With this object in mind we chose 2,2′-bipyridine-4-monoboronic acid (bpymb) and



bpydb



bpymb

2,2′-bipyridine-4,4′-diboronic acid (bpydb) as an '*interface*': since tris(2,2′-bipyridine: bpy)–metal complexes have inherent Δ *vs.* Λ chirality, two pyridine rings in bpydb may be asymmetrically oriented by the formation of a cyclic 1 : 1 complex with saccharides.[12] This saccharide-induced chiral orientation of this ligand should eventually lead to the enantiomeric excess of either Δ- or Λ-isomer in the resultant metal complexes. If this idea really works, it follows that one can achieve the process (i)→(ii)→(iii) using bpydb as an '*interface*' to transmit the saccharide structure to the metal complex chirality.[13,14]

Results and discussion

Determination of the pK_a values and saccharide-induced CD spectra of bpymb and bpydb

To find out the pH range useful for saccharide recognition, pK_a values for bpymb and bpydb were determined. Fig. 1 shows a

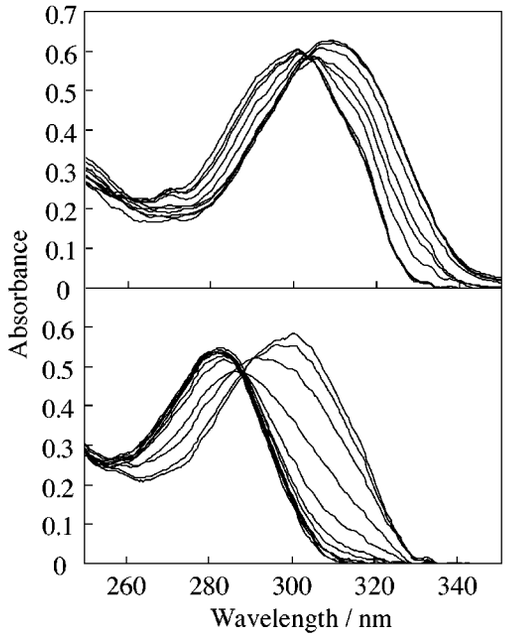
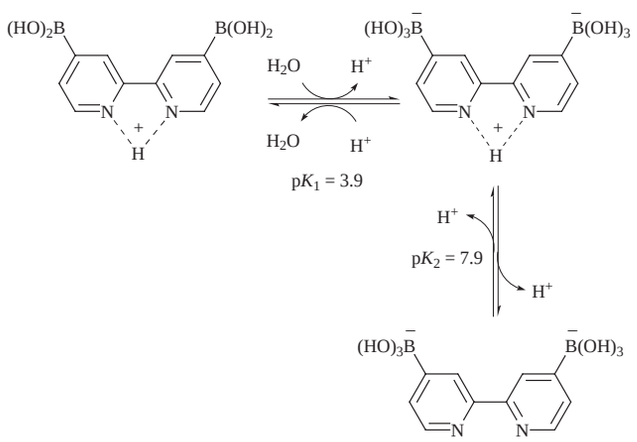


Fig. 1 Phototitration of bpydb (6.00×10^{-5} mol dm^{-3}) at 25 °C: buffer concentration 50 mmol dm^{-3} (for details see Experimental section).

pH-dependent absorption spectral change in bpydb which is a more important ligand than bpymb for the present purpose. For the pH range 1.00–6.00 a tight isosbestic point appears at 289.5 nm whereas for the pH range 6.50–12.00 another tight isosbestic point appears at 286.0 nm. The results indicate that three species which can be differentiated by phototitration exist in bpydb. It is known that pyridine-4-boronic acid (pymb) has pK_{a1} = 3.6 and pK_{a2} = 7.9 which are assigned to OH^--adduct formation with pymbH^+ to yield a zwitterionic species and deprotonation to yield an anionic species, respectively. Hence, the pH-dependent acid dissociation for bpydb can be expressed as in Scheme 1. A plot of A_{320} *versus* pH is shown in Fig. 2. From the analysis of this plot the pK_{a1} and pK_{a2} for bpydb can be estimated to be 3.6 and 7.9, respectively.



Scheme 1

Bpymb also showed the similar pH-dependent spectral change with a tight isosbestic point at 295.5 nm for pH 1.53–6.00 and another tight isosbestic point at 286.0 nm for pH 6.50–11.00. A plot of A_{304} *versus* pH is shown in Fig. 3. From analysis of this plot the pK_{a1} and pK_{a2} can be estimated to be 3.8 and 7.2, respectively (Scheme 2).

It is known that the boronic acid group forms stable saccharide complexes at pH regions where the group can exist as its OH^--adduct. The foregoing pK_{a1} values indicate that the boronic acid groups in bpymb and bpydb are already converted

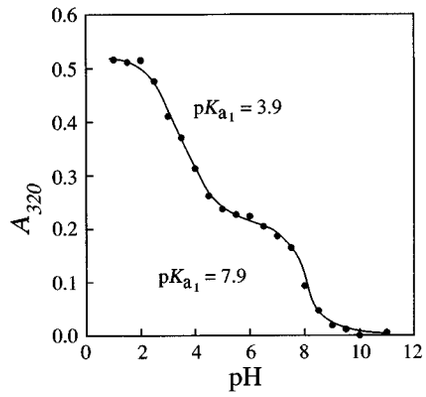


Fig. 2 Plot of A_{320} *vs.* pH for bpydb.

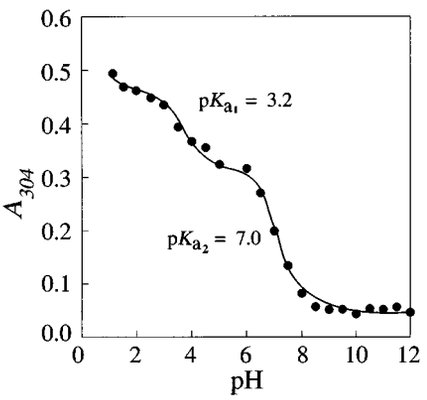
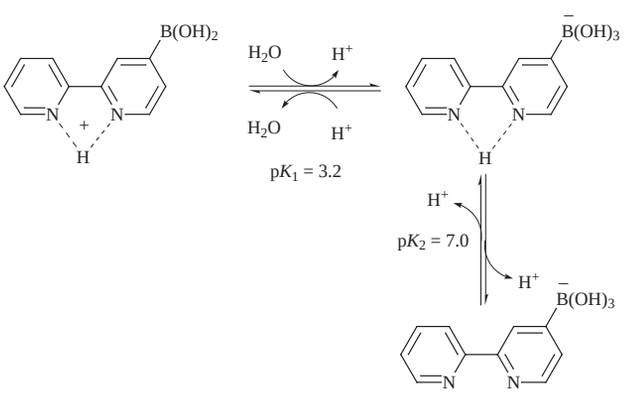


Fig. 3 Plot of A_{304} *vs.* pH for bpymb.



Scheme 2

to the OH^--adducts at neutral pH and, therefore, can form the stable complexes with saccharides. This is a large advantage of bpymb and bpydb as an interface for saccharides.

Chiral orientation of ligands by the saccharide-binding

Previously, we designed diphenyl-3,3′-diboronic acid for the detection of disaccharides.[15] The distance between the two boronic acids (*ca.* 7.4 Å) is comparable with or a little shorter than that between 1,2-*cis*-diol and 4′-OH·5′-CH_2OH in disaccharides with an extended conformation (*ca.* 8.7 Å). As expected, the two boronic acids were bridged by certain disaccharides and the resultant disaccharide-containing macrocycles became CD-active because of a chiral twist of the two phenyl rings. From the sign and the intensity of the CD spectra it is possible to distinguish these disaccharides by CD spectroscopy. Strangely, some monosaccharides (*e.g.*, D-glucose), the molecular size of which is apparently smaller than the diboronic acid in diphenyl-3,3′-diboronic acid, could make

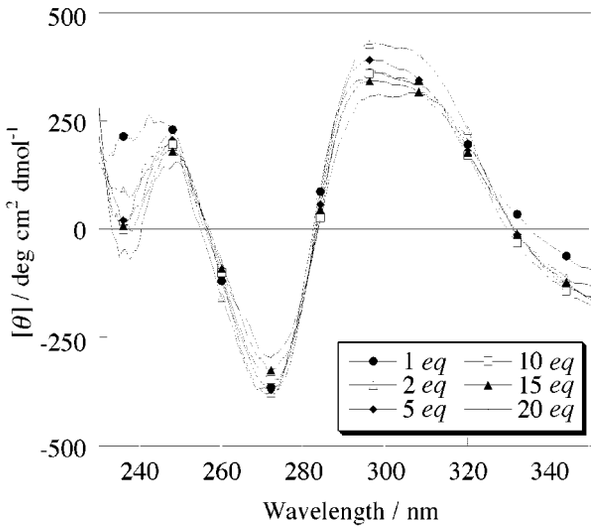


Fig. 4 CD spectra of bpydb (1.69×10^{-2} mol dm^{-3}) in the presence of D-glucose (0–3.38×10^{-1} mol dm^{-3}): water (pH 7.5 with 0.050 mol dm^{-3} MOPS)–methanol = 1 : 1 v/v, 4 °C, 0.2 mm cell width.

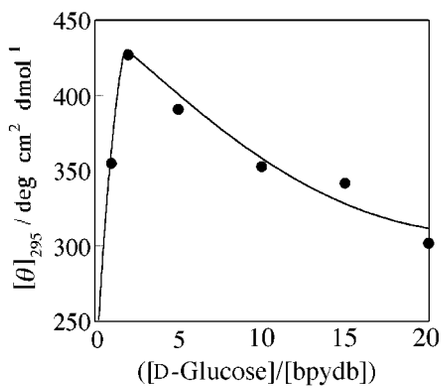


Fig. 5 Plot of $[\theta]_{295}$ *vs.* the D-glucose concentration: the bpydb concentration was kept constant (1.69×10^{-2} mol dm^{-3}). Other conditions are recorded in the Fig. 4 caption.

the complexes CD-active.[15] Examination by Corey–Pauling–Koltun (CPK) molecular models and MM3 computational studies suggest that when 1,2-*cis*-diol forms a cyclic ester with one boronic acid group, 6-OH can reach another boronic acid group:[15] in particular, 6-OH in the furanose form can complex with another boronic acid group.[16] Hence, it can be postulated that the origin of the CD activity induced by monosaccharides also stems from the formation of saccharide-containing macrocycles.

As shown in Fig. 4, bpydb yielded a CD-active species in the presence of D-glucose. Since the wavelength at $\theta = 0$ (283 nm) is comparable with the λ_{max} in the absorption spectrum at the same pH (see Fig. 1), one can observe that the CD spectra feature the exciton coupling band consisting of the first positive Cotton effect and the second negative Cotton effect. This CD sign implies that two pyridine rings are twisted in a clockwise direction ((*R*)-chirality) by D-glucose. In Fig. 5, the CD intensity ($[\theta]_{295}$) is plotted against the D-glucose concentration. It is seen from Fig. 5 that the $[\theta]_{295}$ first increases at [D-glucose]/[bpydb] < 2 and then decreases with increasing D-glucose concentration. This kind of biphasic dependence has frequently been observed for the saccharide-binding to diboronic acid receptors and can be rationalized in terms of a stoichiometrical change from a cyclic 1 : 1 to a noncyclic 1 : 2 diboronic acid–saccharide complex. To obtain explicit evidence for the stoichiometry we applied a Job plot to this system (Fig. 6). Fig. 6 clearly shows that a maximum $[\theta]_{295}$ value appears at [D-glucose]/([D-glucose] + [bpydb]) = 0.5, supporting the idea that the CD-

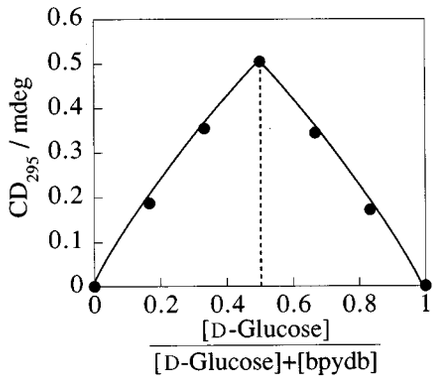
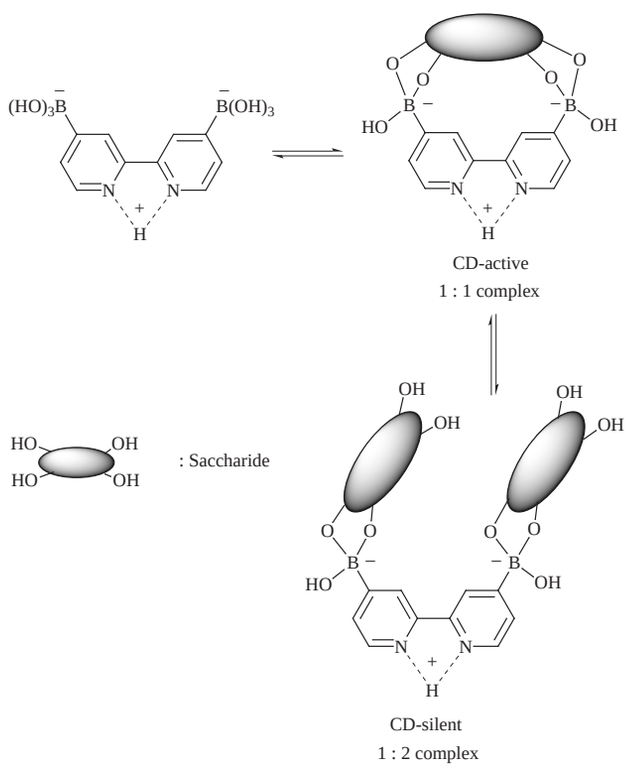


Fig. 6 Job plot: the sum of [D-glucose] and [bpydb] is kept constant (1.69×10^{-2} mol dm^{-3}). Other conditions are recorded in the Fig. 4 caption.

active species is a cyclic 1 : 1 bpydb–D-glucose complex. Based on the foregoing findings, one can propose that D-glucose is bound to bpydb according to Scheme 3. This view was further



Scheme 3

supported by the fact that bpymb does not give the CD-active species in the presence of any saccharides.

The CD spectra of bpydb complexes with several D-monosaccharides and one disaccharide (D-cellobiose) are shown in Fig. 7. As shown in Fig. 7(a), most D-monosaccharides gave a positive exciton coupling band as D-glucose did. The result implies that in general, D-monosaccharides forming cyclic 1 : 1 complexes with bpydb tend to twist the two pyridine rings in a clockwise direction ((*R*)-chirality). D-monosaccharides which gave CD spectra different from the typical positive exciton coupling band are summarized in Fig. 7(b). For the bpydb–D-galactose complex the first positive Cotton effect at around 310 nm could not be observed clearly and the second negative Cotton effect at around 270 nm was weaker than those for other bpydb–D-monosaccharide complexes. The bpydb–D-fucose complex gave more complicated CD bands. Conceivably, the complexity is due to the formation of a few different complex

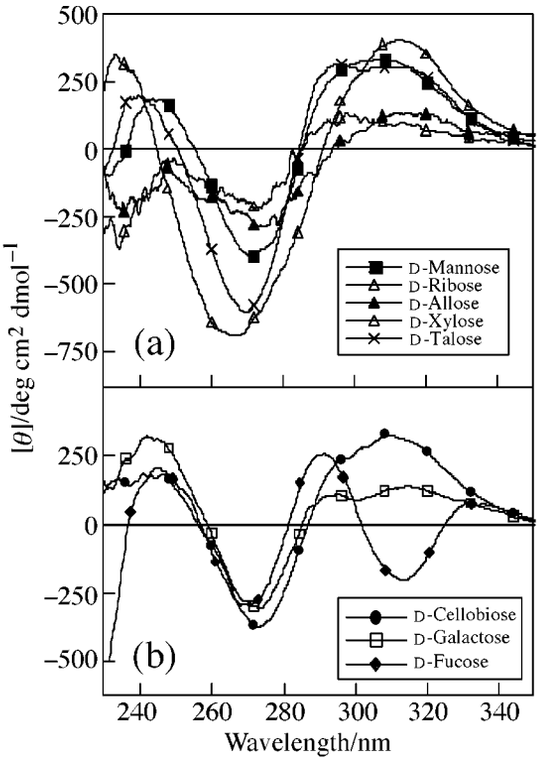


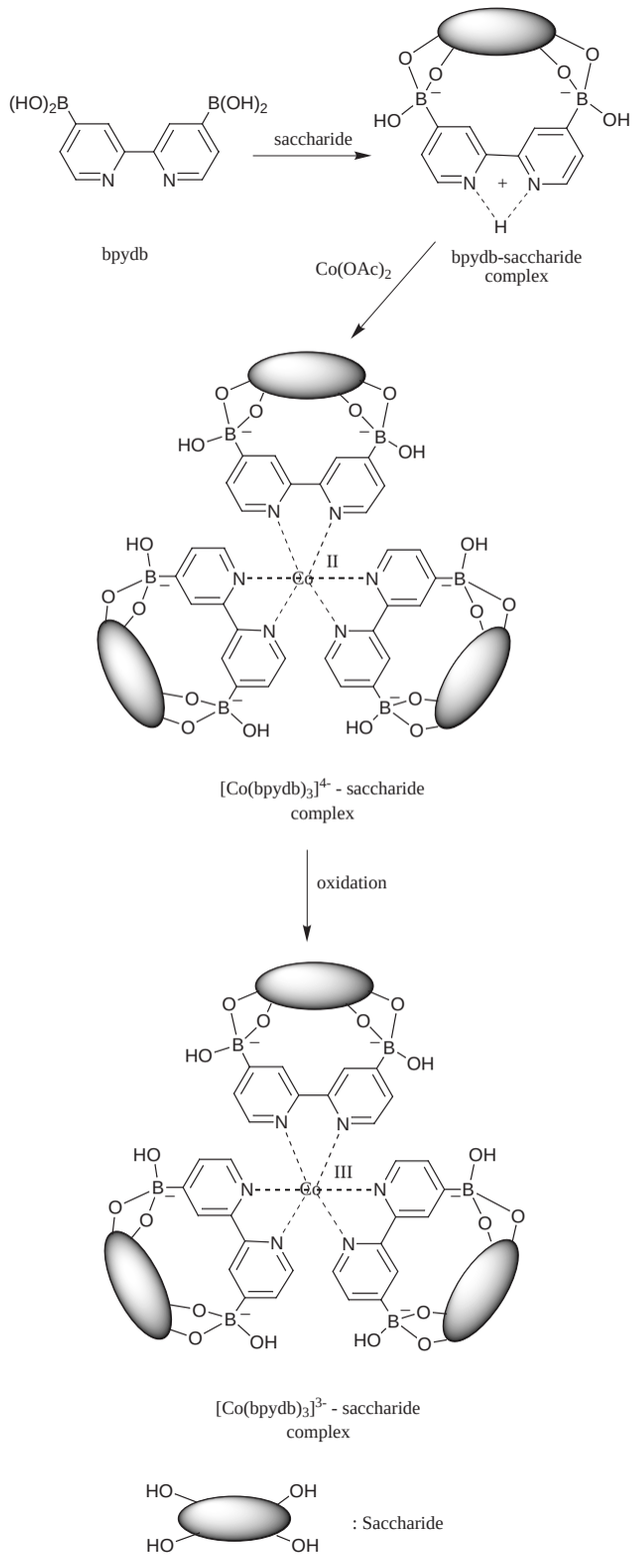
Fig. 7 CD spectra of bpydb–monosaccharide complexes with a (*R*)-chirality exciton coupling band (a) and those with unusual exciton coupling bands and a bpydb–D-cellobiose (disaccharide) complex (b): [bpydb] = 1.69×10^{-2} mol dm^{-3}, [saccharide] = 3.38×10^{-2} mol dm^{-3}. Other conditions are recorded in the Fig. 4 caption.

species. On the other hand, D-cellobiose (disaccharide) also gave a positive exciton coupling band with bpydb.

The foregoing results indicate that the bpydb ligand can be converted to a chiral atropisomer by an intramolecularly-bridged saccharide prior to the metal complex formation. Next, we estimated the possibility of this saccharide-induced chirality being transcripted to the Δ *vs.* Λ chirality ratio of the bpydb metal complexes.

Evaluation of the transcription methods

Previously, we tested the above-mentioned working hypothesis with the Fe^{II} complexes.[12] The reasons why we chose Fe^{II} were (i) Fe^{II} tends to selectively afford the tris-bpy-coordinated $[Fe^{II}(bpy)_3]^{2+}$ species with bpy in aqueous solution, (ii) there is a precedent for successful optical resolution of Δ- and Λ-$[Fe^{II}(bpy)_3]^{2+}$ complexes and (iii) the Fe^{II} complexes usually give a relatively strong absorbance in the MLCT region.[17] Although strong CD bands were observed in the MLCT region for $[Fe^{II}(bpydb)_3]^{4-}$ in the presence of several saccharides, the CD sign could be easily reversed by the addition of the enantiomeric saccharides even at 4 °C.[12] The result implies that in these Fe^{II} complexes racemization between the Δ- and the Λ-isomer can easily occur. To transmit the saccharide chirality one should adopt some substitution-inactive metal complex. Ru^{II} can be such a candidate metal ion, but the Ru^{II} complexes can be prepared only at high temperature where the chirality control is energetically disadvantageous. To overcome this dilemma we contrived the reaction scheme depicted in Scheme 4. Firstly, bpydb (or bpymb: hereafter, the method for bpydb is mainly described but that for bpymb is basically the same) and saccharide were dissolved in a water (pH 7.4 with 1.7×10^{-2} mol dm^{-3} MOPS buffer)–methanol (1 : 1 v/v) solution (1.0 ml), and then the solution was mixed with a water–methanol (1 : 1 v/v) solution (1.0 ml) containing $Co(OAc)_2$ at the appropriate temperature. The reaction mixture was stirred at this temperature for 2 days under a nitrogen atmosphere. As $[Co^{II}(bpy)_3]^{2+}$



Scheme 4

is known to isomerize between Δ- and Λ-isomer (*i.e.*, substitution-active),[17] the $[Co^{II}(bpydb)_3]^{4-}$-saccharide complex should reach some Δ *vs.* Λ equilibrium under the influence of the added saccharide. Then, the $[Co^{II}(bpydb)_3]^{4-}$-saccharide complex was oxidized to the $[Co^{III}(bpydb)_3]^{3-}$-saccharide complex by bubbling O_2 into this solution for 48 h. As $[Co^{III}(bpydb)_3]^{3-}$ is substitution-inactive, the Δ *vs.* Λ ratio has been fixed at this step. By this method one can prepare the substitution-inactive Co^{III} complexes in the presence of saccharides.

It is known that a redox couple of $[Co^{II}(bpy)_3]^{2+}$/$[Co^{III}(bpy)_3]^{3+}$ has $E_{1/2}$ 0.34 V and the $[Co^{II}(bpy)_3]^{2+}$ complex is slowly

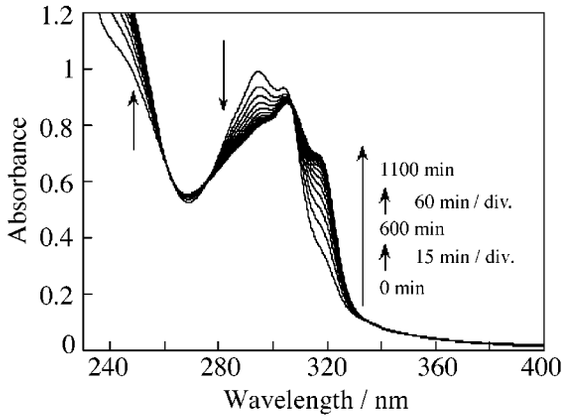


Fig. 8 Absorption spectral change for the dioxygen-oxidation of $[Co^{II}(bpymb)_3]^-$ (6.00×10^{-5} mol dm^{-3}) to $[Co^{III}(bpymb)_3]$: 25 °C, pH 7.0 with 5.0×10^{-2} mol dm^{-3} phosphate buffer.

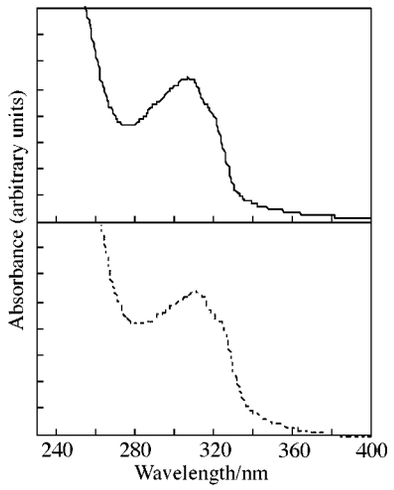


Fig. 9 Absorption spectra of authentic $[Co^{III}(bpydb)_3]^{3-}$ (dotted line) and $[Co^{III}(bpydb)_3]^{3-}$ prepared by dioxygen-oxidation of $[Co^{II}(bpydb)_3]^{4-}$ (solid line). The measurement conditions are recorded in the Fig. 8 caption.

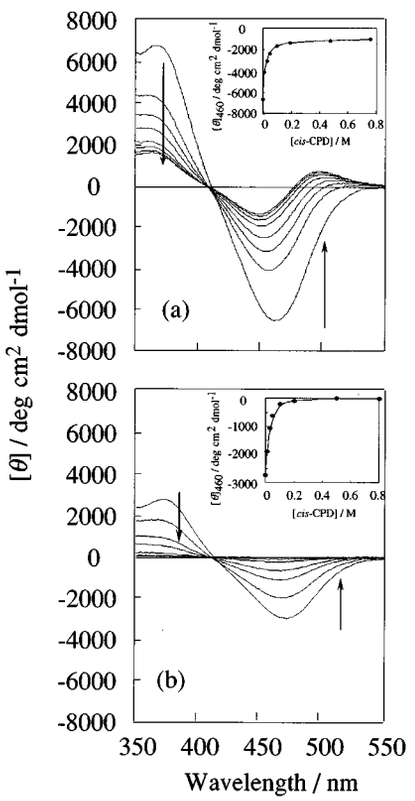


Fig. 10 CD spectra of $[Co^{III}(bpydb)_3]^{3-}$ (5.56×10^{-4} mol dm^{-3}) and the influence of added *cis*-CPD at 25 °C: (a) Sample A, [D-glucose] = 3.38 mmol dm^{-3}, [*cis*-CPD] = 0, 10, 30, 50, 100, 200, 500, 800 mmol dm^{-3} (from bottom to top at 460 nm); (b) Sample B, [D-glucose] = 3.38 mmol dm^{-3}, [*cis*-CPD] = 0, 10, 30, 50, 100, 200, 500, 800 mmol dm^{-3} (from bottom to top at 460 nm).

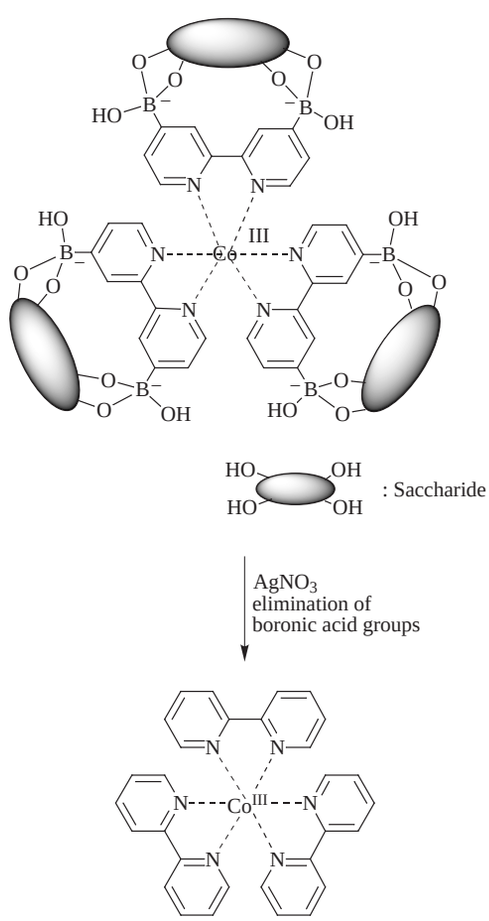
oxidized by dioxygen.[18] This oxidation is characterized by a red shift of the absorption maximum from 301 nm to 317 nm.[18] We measured an absorption spectral change for the oxidation of $[Co^{II}(bpymb)_3]^-$ and found a similar red shift from 307 nm (for the Co^{II} complex) to 317 nm (for the Co^{III} complex) under the present measurement conditions. The CV measurements of $[Co^{II}(bpymb)_3]^-$ resulted in a reversible redox peak at 0.011 V (25 °C, pH 7.0 with 5.0×10^{-2} mol dm^{-3} phosphate buffer, $[Co^{II}(bpymb)_3]^- = 7.50 \times 10^{-4}$ mol dm^{-3}, sweep speed 20 mV s^{-1}). Thus, the $[Co^{II}(bpymb)_3]^-$ complex should be also oxidized by dioxygen. Fig. 8 shows an absorption spectral change of $[Co^{II}(bpymb)_3]^-$ in an aerobic solution. It is seen from Fig. 8 that the λ_{max} peak at 294 nm disappears with the appearance of a new λ_{max} peak at 318 nm and that the spectral change holds a few tight isosbestic points. The final spectrum after 12 h was ascribable to $[Co^{III}(bpymb)_3]$. In the subsequent experiments, therefore, we analyzed the CD spectra of the solutions dioxygen-oxidized for 48 h. On the other hand, the dioxygen-oxidation of $[Co^{II}(bpydb)_3]^{4-}$ was so fast that the spectral change could not be followed by the conventional spectroscopic method. In the CV measurements, the sharp redox peak did not appear in the range of −0.4–0.4 V. Judging from the fact that the $E_{1/2}$ value for $[Co^{II}(bpymb)_3]^-$ is more negative than that for $[Co^{II}(bpy)_3]^{2+}$, $[Co^{II}(bpydb)_3]^{4-}$ should possess an $E_{1/2}$ value more negative than $[Co^{II}(bpymb)_3]^-$ (*i.e.*, more negative than 0.011 V). Because of this negative $E_{1/2}$ shift, $[Co^{II}(bpydb)_3]^{4-}$ has become sensitive to dioxygen-oxidation. Thus, completion of this oxidation process was confirmed by the following lines of indirect evidence: (i) the absorption spectrum of the resultant complex is the same as that of the authentic $[Co^{III}(bpydb)_3]^{3-}$ complex prepared from $[Co^{III}Cl(NH_3)_5]^{2+}$ and bpydb (Fig. 9), (ii) the absorption spectrum is unaffected by further oxidation with H_2O_2, (iii) the complex is ESR-silent (because Co^{II} is paramagnetic whereas Co^{III} is diamagnetic) and (iv) the ^{1}H NMR spectrum does not show any indication that the complex is paramagnetic (*e.g.*, line-broadening, unusual chemical shift, *etc.*). We mixed the bpydb–saccharide complex and $Co^{II}(OAc)_2$ under the anaerobic conditions and introduced dioxygen after 10 min so that Co^{II} could form the $[Co^{II}(bpydb)_3]^{3-}$–saccharide complex. As $[Co^{III}(bpymb)_3]^-$ and $[Co^{III}(bpydb)_3]^{3-}$ are substitution-inactive,[17] the Δ *vs.* Λ ratio has been fixed at these oxidation steps.

CD spectral measurements

The CD spectrum of the $[Co^{III}(bpydb)_3]^{3-}$–saccharide complex obtained at 4 °C in the presence of D-glucose (Sample A) is shown in Fig. 10(a). We also prepared a complex (Sample B) in which D-glucose was added after $[Co^{II}(bpydb)_3]^{4-}$ was oxidized to $[Co^{III}(bpydb)_3]^{3-}$ (Fig. 10(b)). Although both samples are CD-active, one must consider that the CD band arising from Δ *vs.* Λ chirality overlaps with the saccharide-induced CD band. In fact, a mixture of racemic $[Co^{III}(bpydb)_3]^{3-}$ and D-glucose resulted in a CD spectrum similar to Fig. 10(b). To estimate whether the CD spectra truly contain the CD band arising from Δ *vs.* Λ chirality we added an excess amount of optically-inactive *cis*-cyclopentane-1,2-diol (*cis*-CPD): this compound shows a high affinity with boronic acids and can competitively substitute D-glucose bound to the boronic acid groups in $[Co^{III}(bpydb)_3]^{3-}$.[19] As shown in Fig. 10(b), the CD

band of Sample B decreased with increasing *cis*-CPD concentration and almost disappeared at [*cis*-CPD]/[D-glucose] = 25. In contrast, the CD band of Sample A also decreased with increasing *cis*-CPD concentration but remained still CD-active with $[\theta]_{460}$ = 1100 deg cm^2 dmol^{-1} even in the presence of excess *cis*-CPD. The difference clearly indicates that Sample B consists of a 1:1 racemic mixture of Δ- and Λ- isomers whereas in Sample A one isomer exists in excess over the other.

Similar CD spectra were also observed for the $[Co^{III}(bpymb)_3]^-$–D-glucose complexes. When excess *cis*-CPD was added, the CD band of the complex prepared in a manner similar to Sample B disappeared whereas the CD band of the complex prepared in a manner similar to Sample A remained although the intensity ($[\theta]_{460}$ = 180 deg cm^2 dmol^{-1}) was weaker than that for Sample A in the $[Co^{III}(bpydb)_3]^{3-}$–D-glucose complex. To estimate the enantiomeric excess (e.e.) of the $[Co^{III}(bpydb)_3]^{3-}$–saccharide complexes we applied a HPLC method with chiral-packed columns or a ^{1}H NMR spectroscopic method with chiral shift reagents but unfortunately these methods were not successful. These methods are not suitable to optical resolution of the metal complex containing six boronic acid groups. It is known that a boronic acid group in phenylboronic acid can be eliminated by treatment with $AgNO_3$.[20] We applied this method to the present metal complexes and tried to determine the e.e. by comparison with authentic Δ- and Λ-$[Co^{III}(bpy)_3]^{3+}$.[21] Thus, $AgNO_3$ (500 mg, 2.9 mmol) was added to the Sample A solution and the mixture was stirred at room temperature. The progress of the reaction was monitored by HPLC (Zorbax ODS, water–methanol = 1:4 v/v). It showed that both $[Co^{III}(bpymb)_3]$ and $[Co^{III}(bpydb)_3]^{3-}$ are quantitatively converted to $[Co^{III}(bpy)_3]^{3+}$ after one day (Scheme 5).[18,21] After membrane filtration (Millipore LCR 13-LH), the filtrate was purified using gel filtration (Toyopearl HW-40, water–methanol = 1:1 v/v). The yields of recovered $[Co^{III}(bpy)_3]^{3+}$ after gel filtration were higher than 80%. The CD spectrum of $[Co^{III}(bpy)_3]^{3+}$ obtained from the $[Co^{III}(bpydb)_3]^{3-}$–D-glucose complex is shown in Fig. 11. By comparison with the CD spectrum of optically-pure Δ-$[Co^{III}(bpy)_3]^{3+}$ [21] the optical purity of this sample was determined to be 47% e.e. (Δ excess). By a similar operation, the optical purity of $[Co^{III}(bpy)_3]^{3+}$ obtained from the $[Co^{III}(bpymb)_3]$–D-glucose complex was estimated to be 16% e.e. (Δ excess). The result indicates that bpydb is a better ligand than bpymb for chiroselective transcription. We repeated the sample preparation from $[Co^{III}(bpydb)_3]^{3-}$ in the presence of various saccharides and determined the optical purities of the resultant $[Co^{III}(bpy)_3]^{3+}$ by CD spectroscopy. The results are summarized in Table 1. Examination of Table 1 reveals that the highest optical yield is obtained from glucose: D- and L-glucose yield the Δ- and Λ-enantiomer in excess, respectively both in 47% e.e. Hence, the optimization was carried out with $[Co^{II}(bpydb)_3]^{4-}$ and D-glucose which gave the highest e.e. among the saccharides tested.



Scheme 5

Table 1 Configuration and enantiomeric excess of $[Co^{III}(bpy)_3]^{3+}$ obtained from the reaction of $[Co^{III}(bpydb)_3]^{3-}$ and $AgNO_3$

Saccharide	Configuration	e.e. (%)
D-Glucose	Δ	47
L-Glucose	Λ	47
D-Galactose	Δ	5
D-Mannose	Δ	10
D-Talose	Δ	2
D-Allose	—	0
D-Fructose	Λ	5
D-Xylose	Δ	6
D-Fucose	Λ	13
D-Ribose	Δ	2
D-Cellobiose	Δ	2

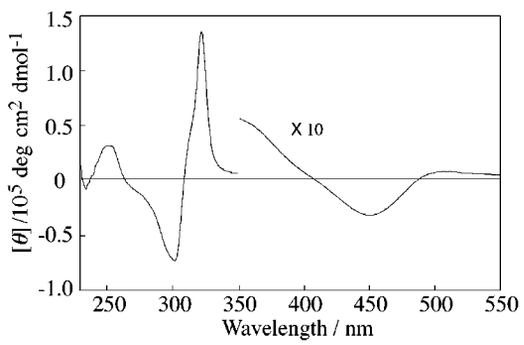


Fig. 11 CD spectrum of $[Co^{III}(bpy)_3]^{3+}$ (1.00×10^{-3} mol dm^{-3}) obtained from Sample A ([D-glucose] = 3.38 mmol dm^{-3} in feed) after elimination of boronic acid groups by $AgNO_3$: 25 °C, water–methanol = 1:1 v/v.

Fig. 12(a) shows the influence of the D-glucose concentration (in feed) on the e.e. of Δ-$[Co^{III}(bpy)_3]^{3+}$. The maximal e.e. (47% e.e.) appeared at [D-glucose] = 5.66×10^{-3} mol dm^{-3}, which corresponds to [D-glucose]/[bpydb] = 2.0. This ratio is the same as that observed for the plot of the CD intensity of bpydb *vs.* [D-glucose] (see Fig. 5). Since bpydb and D-glucose form a cyclic 1:1 complex (see Fig. 6), the result supports the view that the stoichiometry of bpydb/D-glucose in the $[Co^{III}(bpydb)_3]^{3-}$–D-glucose complex should be also 1:1 at the maximal CD intensity. Fig. 12(b) shows the influence of the reaction temperature on the e.e. of Δ-$[Co^{III}(bpy)_3]^{3+}$. It is seen from Fig. 12(b) that *the e.e. increases with lowering the reaction temperature and at −25 °C it even reaches 79% e.e.* Under similar conditions in the presence of L-glucose we could obtain Λ-$[Co^{III}(bpy)_3]^{3+}$ in 79% e.e.

Comments on the mechanism of chiroselective transcription

The data collected in Table 1 indicate that in general,

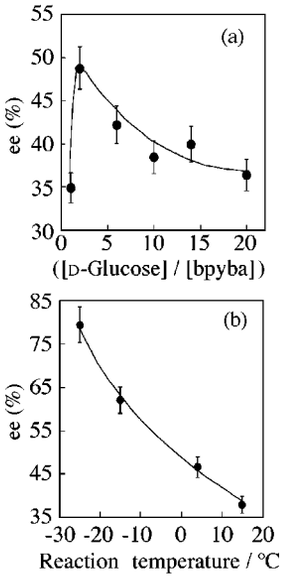


Fig. 12 Influence of the D-glucose concentration (a) and the reaction temperature (b) on the e.e. of $[Co^{III}(bpy)_3]^{3+}$.

D-saccharides tend to orientate bpydb to form the Δ enantiomers in preference to the Λ enantiomers. The reason for this is not clear yet. However, the comparison of the CD spectral data of the bpydb–D-saccharide complexes with the Δ *vs.* Λ preference supports the view that the chiral twist of the two pyridine rings in bpydb by D-saccharides is the origin of the chirality creation in the final $[Co^{III}(bpy)_3]^{3+}$ complex, because (i) the bpydb–D-fucose complex which has a CD spectrum different from the others (Fig. 7(b)) results in Λ enantiomers with 13% e.e., (ii) D-allose and D-ribose which only give weak CD intensity with bpydb (Fig. 7(a)) result in a very low e.e. (0–2% e.e.) and (iii) the highest e.e. value for $[Co^{III}(bpydb)_3]^{3-}$ is obtained at the D-glucose concentration (*i.e.*, [D-glucose]/[bpydb] = 2.0) where the highest CD intensity for the bpydb–D-glucose complex is observed.

It is also true, however, that the chirality creation is not only due to the chiral twist of the two pyridine rings, because (i) the magnitude of the e.e. values is not necessarily correlated with the CD intensity of the bpydb–D-saccharide complexes and (ii) bpymb which cannot form the D-saccharide-containing cyclic complex also yields Δ-excess $[Co^{III}(bpy)_3]^{3+}$ in the presence of D-glucose although the e.e. is lower than that for bpydb. These findings support the view that steric crowding among saccharide-carrying bpymb or bpydb and the inter-ligand bridging by saccharides in the Co^{II} complexes also affect the Δ *vs.* Λ preference. We now consider that the chiral twist of the two pyridine rings by intra-ligand bridging is the primary factor and the other effects in the Co^{II} complex form the secondary factor.

Conclusions

The foregoing results clearly establish that the saccharide-templated synthesis is useful as a new concept for the preparation of chiral tris(2,2′-bipyridine)–metal complexes. Furthermore, the Δ *vs.* Λ equilibrium can be shifted in either direction by the selection of saccharide enantiomers. The chemistry of chiral tris(2,2′-bipyridine)–metal complexes has become a very active area of research in relation to asymmetric synthesis, asymmetric memory transduction, nonlinear optics, photo-induced electron or energy transfer, *etc*.[22–24] However, these fields have always been hampered by difficulty in the preparation of the chiral metal complexes. We believe that the present method provides an important breakthrough for these advanced fields of science.

Experimental

Materials

2,2′-Bipyridine-4-boronic acid (bpymb) was synthesized from 2,2′-bipyridine *via* its *N*-oxide intermediate. Since the preparation of 4-nitro-2,2′-bipyridine-*N*-oxide has already been reported,[25] the synthetic procedures starting from this compound are described below. 2,2′-Bipyridine-4,4′-diboronic acid (bpydb) was also synthesized from 2,2′-bipyridine. In the synthetic route the preparation of 4,4′-dibromo-2,2′-bipyridine was already reported, so that the synthetic procedures starting from this compound are described below.

4-Bromo-2,2′-bipyridine-*N*-oxide. 4-Nitro-2,2′-bipyridine-*N*-oxide (5.2 g, 23.9 mmol) was dissolved in acetic acid (50 ml) containing acetyl bromide (26.0 ml, 35.2 mmol) and the solution was refluxed for 9 h under a nitrogen atmosphere. The progress of the reaction was monitored by a TLC method (silica gel, $R_f = 0.1$, chloroform). After cooling, the solution was poured into an ice–water mixture (100 g) and the pH of the aqueous phase was adjusted to 11 with aqueous KOH solution. The product was extracted from the aqueous phase with chloroform. The organic solution was dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to flush column chromatography (silica gel, chloroform) for the purification: (5.3 g, 89%), mp 65.8–66.2 °C; δ_H [250 MHz; $CDCl_3$] 7.37–7.44 (2H, m, 5-H, 4′-H), 7.85 (1H, t, *J* 7.1, 8.3, 5′-H), 8.26 (1H, d, *J* 7.0, 3′-H), 8.40 (1H, s, 3-H), 8.75 (1H, d, *J* 8.7, 6-H), 8.90 (1H, d, *J* 8.1, 6′-H). This product was used for the next reaction without further purificaton.

4-Bromo-2,2′-bipyridine. 4-Bromo-2,2′-bipyridine-*N*-oxide (5.3 g, 21.1 mmol) and PBr_3 (7.0 ml, 73.9 mmol) were dissolved in chloroform (50 ml) and the solution was refluxed for 4 h under a nitrogen atmosphere. The progress of the reaction was monitored by a TLC method (silica gel, $R_f = 0.2$, chloroform). After cooling, the solution was poured into an ice–water mixture and the pH of the aqueous phase was adjusted to 11 with aqueous KOH solution. The product was extracted with chloroform, the organic layer being dried over $MgSO_4$. The solution was evaporated to dryness and the residue was subjected to flush column chromatography (silica gel, chloroform) for the purification: (2.5 g, 50%), mp 52.9–53.6 °C (Found: C, 51.26; H, 3.01; N, 11.96. $C_{10}H_7N_2Br$ requires C, 51.26; H, 3.06; N, 11.95%); δ_H [250 MHz; $CDCl_3$] 7.34 (1H, dd, *J* 4.8, 7.7, 5′-H), 7.48 (1H, d, *J* 5.5, 5-H), 7.83 (1H, t, *J* 8.1, 7.6, 4′-H), 8.39 (1H, d, *J* 8.1, 3′-H), 8.49 (1H, d, *J* 5.2, 6-H), 8.63 (1H, s, 3-H), 8.69 (1H, d, *J* 4.8, 6′-H).

2,2′-Bipyridine-4-boronic acid (bpymb). 4-Bromo-2,2′-bipyridine (1.0 g, 4.25 mmol) was dissolved in anhydrous diethyl ether (80 ml) in a nitrogen-flushed flask and the solution was cooled to −100 to −110 °C with a N_2 (liq.)–methanol bath. An *n*-hexane solution (3.12 ml) containing *n*-BuLi (1.5 mol dm^{-3}, 4.68 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 30 min. Trimethyl borate (0.49 ml, 4.68 mmol) was added: the mixture was stirred for 1 h at this temperature and then for one day while gradually raising the reaction temperature to room temperature. The reaction mixture was concentrated to dryness, the residual solid being dissolved in methanol. The methanol solution was poured into acetone, the precipitate being recovered by filtration: (450 mg, 52%), mp (decomp.) >250 °C (Found: C, 59.87; H, 4.60; N, 13.89. $C_{10}H_9BN_2O_2$ + 0.05 CH_3OH requires C, 60.67; H, 4.21; N, 13.45%); δ_H [250 MHz; CD_3OD] 7.38 (1H, dd, *J* 4.6, 8.3, 5′-H), 7.58 (1H, d, *J* 4.5, 5-H), 7.90 (1H, t, *J* 7.6, 8.5, 4′-H), 8.08 (1H, d, *J* 7.8, 3′-H), 8.32 (1H, s, 3-H), 8.38 (1H, d, *J* 4.5, 6′-H), 8.62 (1H, d, *J* 4.4, 6-H).

2.2′-Bipyridine-4,4′-diboronic acid (bpydb). This compound was synthesized from 4,4′-dibromo-2,2′-bipyridine in a manner similar to that described for bpymb except for the reaction solvent (anhydrous THF was used instead of anhydrous diethyl ether). The reaction was stopped by the addition of water (1.0

ml). The gelatinous reaction mixture thus obtained was concentrated *in vacuo* to dryness, the solid residue being dissolved in methanol. The methanol solution was poured into acetone, the precipitate being recovered by filtration. Finally, the product was washed with a small amount of methanol and then with diethyl ether: (700 mg, 80%), mp (decomp.) >250 °C (Found: C, 51.11; H, 6.44; N, 7.45. $C_{16}H_{24}B_2Li_2N_2O_6$ requires C, 51.03; H, 6.03; N, 7.35%); δ_H [250 MHz; CD_3OD] 7.54 (2H, d, *J* 4.6, 5,5′-H), 8.16 (2H, s, 3,3′-H), 8.36 (2H, d, *J* 4.6, 6,6′-H). The elemental analysis data indicates that the boronic acid groups are isolated as $-B^-(OMe)_3$ Li^+. Although these methoxy protons could not be found by ^1H NMR spectroscopy in CD_3OD, they were easily found as CH_3OD (3.34 ppm, integral intensity 18H as a hydrolysis product of $-B^-(OMe)_3$ Li^+) in D_2O.

General procedure for the preparation of $[Co^{III}(bpy)_3]^{3+}$ from $[Co^{III}(bpymb)_3]$ or $[Co^{III}(bpydb)_3]^{3-}$. $AgNO_3$ (500 mg, 2.9 mmol) was added to the sample solution (2.0 ml: pH 7.4 with 5.0×10^{-5} mol dm^{-3} MOPS buffer–methanol (1:1 v/v)) containing a $[Co^{III}(bpymb)_3]$–saccharide complex or a $[Co^{III}(bpydb)_3]^{3-}$–saccharide complex and the mixture was stirred at room temperature for one day. The progress of the reaction was monitored by a HPLC method (Zorbax ODS, water–methanol (1:4 v/v)). It showed that these complexes are quantitatively converted to $[Co^{III}(bpy)_3]^{3+}$ after one day. After membrane filtration (Millipore LCR 13-LH), the filtrate was purified using gel filtration (Toyopearl HW-40, water–methanol (1:1 v/v)). The yields of recovered $[Co^{III}(bpy)_3]^{3+}$ were higher than 80%. The products thus obtained were subjected to the CD measurement.

Miscellaneous. For the phototitration of bpymb and bpydb, the following buffer solutions were used: 50 mmol dm^{-3} HCl for pH 1.0–2.0, 50 mmol dm^{-3} HCOOH for pH 2.5–3.0, 50 mmol dm^{-3} acetate for pH 3.5–5.0, 50 mmol dm^{-3} phosphate for pH 6.5–9.0, 50 mmol dm^{-3} carbonate for pH 9.5–10.5, 50 mmol dm^{-3} NaOH for pH 11.0–12.0. Absorption spectra, CD spectra and ^1H NMR spectra were measured with Hitachi V-3000, Jasco J-720 and Bruker AC-250P spectrometers. HPLC analyses were performed on a Jasco PU-980 pump equipped with a Zorbax ODS column.

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