Chiroselective transcription of the sugar structure to Δ- or Λ-[Co^{III}(bpy)$_3$]$^{3+}$ using a boronic acid–sugar template interaction

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In order to apply boronic acid–saccharide interactions to the chiroselective synthesis of Δ- and Λ-[Co^{III}(bpy)$_3$]$^{3+}$ a saccharide-binding ligand, 2,2′-bipyridine-4,4′-diboronic acid (bpyba) is newly synthesized; the enantiomeric excess under the optimum reaction conditions reached 79% ee!

The recognition of biologically important molecular species by synthetic molecular receptors has gained momentum. Since the chemistry of saccharides plays a significant role in the metabolic pathways of living organisms, the detection of biologically important saccharides is necessary in a variety of medical and industrial contexts. Although hydrogen-bonding interactions play a central role in most reported synthetic receptors,[1] it has recently been shown that boronic acid–saccharide 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 the specific saccharide.[6] 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.[8–10] 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 gifts us with a variety of saccharides with chiral structures. Tris[2,2′-bipyridine(bpy)]–metal complexes have inherent Δ *vs.* Λ chirality. It occurred to us that two pyridine rings may be asymmetrically oriented by a boronic acid–saccharide interaction[11] and the metal complexes thus formed may contain an excess amount of either Δ- or Λ-isomer over the other.[12]

With this object in mind we synthesized 2,2′-bipyridine-4,4′-diboronic acid (bpyba),[13] expecting that the saccharide-induced chiral orientation of this ligand eventually leads to the enantiomeric excess of either Δ- or Λ-isomer in the resultant metal complexes.
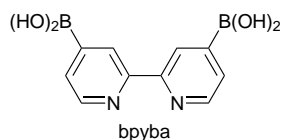
bpyba

To test the above working hypothesis we contrived the following reaction scheme. First, bpyba (6.37 mg, 1.69×10^{-5} mol) and a saccharide (3.38×10^{-5} mol) were dissolved in a water (pH 7.4 with 50 mM 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)$_2$ (1.00 mg, 5.65×10^{-6} mol) at the appropriate temperature. The reaction mixture was stirred at this temperature for 2 days under a nitrogen atmosphere. As [Co^{II}(bpy)$_3$]$^{2+}$ is known to isomerize between Δ- and Λ-isomer (*i.e.* substitution active),[14] the [Co^{II}(bpyba)$_3$]$^{4-}$–saccharide complex should reach some Δ *vs.* Λ equilibrium under the influence of added saccharides. Then, the [Co^{II}(bpyba)$_3$]$^{4-}$–saccharide complex was oxidized to the [Co^{III}(bpyba)$_3$]$^{3-}$–saccharide complex by bubbling O$_2$ into this solution for 48 h. The completion of this oxidation process was confirmed by the following observations: (*i*) the absorption spectrum of the resultant complex is the same as the authentic [Co^{III}(bpyba)$_3$]$^{3-}$ complex prepared from [Co^{III}Cl(NH$_3$)$_5$]$^{2+}$ and bpyba, (*ii*) the absorption spectrum is unaffected by further oxidation with H$_2$O$_2$, (*iii*) the complex is EPR silent 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.*). As [Co^{III}(bpyba)$_3$]$^{3-}$ is substitution-inactive,[14] the Δ *vs.* Λ ratio has been fixed at this step.

The CD spectrum of the [Co^{III}(bpyba)$_3$]$^{3-}$–saccharide complex obtained at 4 °C in the presence of D-glucose (sample A) is shown in Fig. 1(*a*). We also prepared a complex (sample B) in which D-glucose was added after [Co^{II}(bpyba)$_3$]$^{4-}$ is oxidized to [Co^{III}(bpyba)$_3$]$^{3-}$ [Fig. 1(*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 ICD band. In fact, a mixture of racemic [Co^{III}(bpyba)$_3$]$^{3-}$ and D-glucose resulted in a CD spectrum similar to Fig. 1(*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 the high affinity with boronic acids and can competitively substitute D-glucose bound to the boronic acid groups in [Co^{III}(bpyba)$_3$]$^{3-}$.[3–15] As shown in Fig. 1(*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 [θ]$_{460}$ =
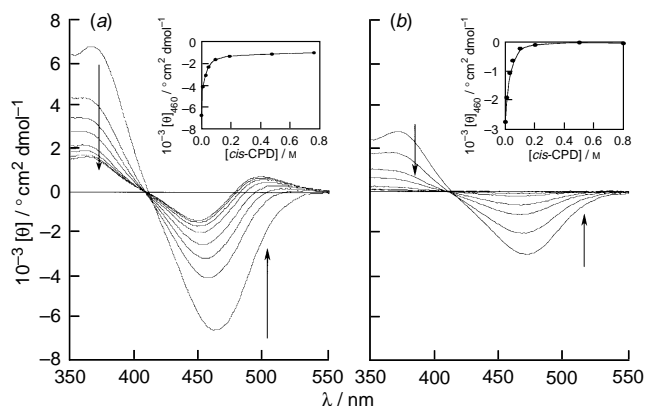

Fig. 1 CD spectra of [Co^{III}(bpyba)$_3$]$^{3-}$ (5.56×10^{-4} M) and the influence of added *cis*-CPD at 25 °C: (*a*) sample A, [D-glucose] = 3.38 mM, [*cis*-CPD] = 0, 10, 30, 50, 100, 200, 500, 800 mM (from bottom to top at 460 nm); (*b*) sample B, [D-glucose] = 3.38 mM, [*cis*-CPD] = 0, 10, 30, 50, 100, 200, 500, 800 mM (from bottom to top at 460 nm)
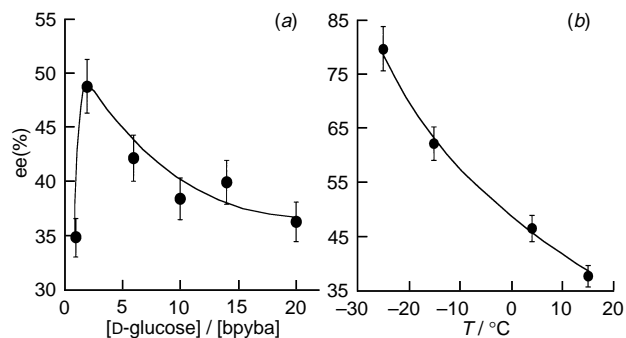
Fig. 2 Influence of the D-glucose concentration (*a*) and the reaction temperature (*b*) on the ee of [Co^{III}(bpy)$_3$]$^{3+}$

1100° cm^2 dmol^{-1} even in the presence of excess *cis*-CPD. The results clearly indicate 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.

To estimate the enantiomeric excess (ee) of the [Co^{III}-(bpyba)$_3$]$^{3-}$–saccharide complexes we applied a HPLC method with chiral-packed columns and a ^{1}H NMR spectroscopic method with chiral shift reagents but failed. It is known that a boronic acid group in phenylboronic acid can be eliminated by treatment with AgNO$_3$.[16] We applied this method to the [Co^{III}(bpyba)$_3$]$^{3-}$–saccharide complexes and tried to determine the ee by comparison with authentic Δ- and Λ-[Co^{III}(bpy)$_3$]$^{3+}$.[17] 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 [Co^{III}(bpyba)$_3$]$^{3-}$ is quantitatively converted to [Co^{III}(bpy)$_3$]$^{3+}$ after one day.[18] After membrane filtration (Millipore LCR 13-LH), the filtrate was purified using gel filtration [Toyopearl HW-40, water–methanol (1 : 1 v/v)]. The yield of recovered [Co^{III}(bpy)$_3$]$^{3+}$ after gel filtration was 80%. The CD spectrum of [Co^{III}(bpy)$_3$]$^{3+}$ was thus obtained. By comparison with the CD spectrum of optically pure Δ-[Co^{III}(bpy)$_3$]$^{3+}$[17] the optical purity of this sample could be determined to be 47% ee (Δ excess). We repeated the sample preparation in the presence of various saccharides and obtained the following results: 47% ee (Λ excess) for L-glucose, 2% ee (Δ excess) for D-ribose, 10% ee (Δ excess) for D-mannose, 2% ee (Λ excess) for D-talose, 6% ee (Λ excess) for D-xylose, 12% ee (Δ excess) for D-maltose, and 3% ee (Δ excess) for D-cellobiose. Further examination was carried out with D-glucose which gave the highest ee among saccharides tested herein.

Fig. 2(*a*) shows the influence of the D-glucose concentration (in feed) on the ee of Δ-[Co^{III}(bpy)$_3$]$^{3+}$. The maximal ee (47%) appeared at [D-glucose] = 5.66 × 10^{-3} M, which corresponds to [D-glucose]/[bpyba] = 2.0. This ratio indicates that the ee of Δ-[Co^{III}(bpy)$_3$]$^{3+}$ becomes maximal when one boronic acid group binds one D-glucose molecule. Fig. 2(*b*) shows the influence of the reaction temperature on the ee of Δ-[Co^{III}(bpy)$_3$]$^{3+}$. It is seen from Fig. 2(*b*) that the ee increases with lowering the reaction temperature and at −25 °C it even reaches 79%. Under the similar conditions in the presence of L-glucose we could obtain Λ-[Co^{III}(bpy)$_3$]$^{3+}$ in 79% ee.

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 endeavour in relation to asymmetric synthesis, asymmetric memory transduction, non-linear optics, photoinduced electron or energy transfer, *etc.*[19–21] 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.

Footnote and References

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