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Copper(II)-mediated chiral helicity amplification and inversion of *meta*-ethynylpyridine polymers with metal coordination sites†

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***meta*-Ethynylpyridine polymers bearing metal coordination sites associate with alkyl glycoside guests to show induced circular dichroism (ICD) bands. The addition of a Cu(II) ion changed the intensity or the sign of these ICD bands. The changes suggested chiral helicity amplification or inversion of the polymers by Cu(II)-mediated cross-linking at the coordinating side chains.**

Helical structures in biopolymers play crucial roles in living systems both for constructing their own higher-order structures and interacting with others.[1] Among them, helices of DNA and peptides are often stabilized by the presence of chemical species with small molecular weights such as metal ions.[1b,c] Metal ion-mediated higher-order architectures also have been seen in synthetic molecules.[2,3] Lehn *et al.* developed double-stranded helicates by spontaneous assembly of oligobipyridine ligands and metal ions.[3a] Yashima *et al.* reported the control of the spring-like motion of double-stranded helicates by the addition and removal of sodium ions.[3h]

Our group has developed 2,6-pyridylene ethynylene "*meta*-ethynylpyridine" polymers and oligomers, which consisted of 4-functionalized pyridine rings linked at their 2,6-positions with acetylene bonds.[4] These polymers and oligomers recognize various kinds of saccharide guests by multiple hydrogen bonds between pyridine nitrogen atoms and hydroxy groups of the guests.[5–7] The resulting complexes form biased helical structures to show circular dichroisms (CDs).[8] Functional groups at the 4-positions on the pyridine units build on extra characteristics such as amphiphilicity[4c,d] and strong basicity[4b] to the polymers and oligomers. Recently, we reported an azacrown-attached *meta*-ethynylpyridine polymer **1** that incorporates additional molecular recognition sites at its side chains[4g] (Fig. 1). When octyl β-D- and L-glucopyranosides were added to a CH_2Cl_2 solution of **1**, a mirror-image pair of induced CD (ICD) bands was observed, indicating that **1** formed chiral helical complexes with the guests. These ICDs were significantly enhanced by the addition of oligoammonium cations. The ICD enhancements would be due to the formation of a pseudopolyrotaxane structure between the azacrown and the oligoammonium moieties, which stabilized the chiral helical complexes by cross-linking the side chains. Herein, we report a new type of *meta*-ethynylpyridine polymers **2–4** with metal-coordination sites (bis(2-methoxyethyl)amino groups) attached through mono-, di-, and tri-oxyethylene spacers at the 4-position of each pyridine unit, respectively (Fig. 1). The coordination of metal ions would be expected to stabilize (or destabilize) the helical structure by cross-linking the side chains much straightforwardly than the pseudopolyrotaxane formation in **1** (Fig. 2).

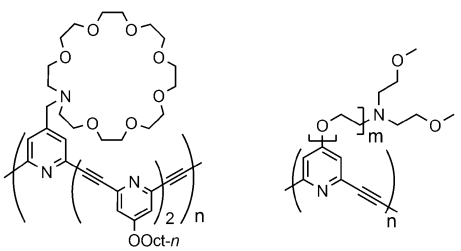

Fig. 1 *meta*-Ethynylpyridine polymers **1–4**.

The polymer **2** was prepared as shown in Scheme 1. Commercially available 2,6-dibromopyridine was converted into 2,6-dibromo-4-nitropyridine (**5**) in three steps.[9] Aromatic substitution on **5** with monosodium ethylene glycolate (ethylene glycol and sodium hydride) gave 2,6-dibromo-4-(2-hydroxyethyloxy)pyridine (**6**). After halogen exchange of **6** into diiodide **7**,[10] the hydroxy group was tosylated to give **8**. Then, a Cu(II)-coordination site was introduced to **8** by the condensation with bis(2-methoxyethyl)amine to afford tertiary amine **9**. Diacetylene **11** was obtained from **9** by the Sonogashira reaction with trimethylsilylacetylene followed by protiodesilylation. The final co-polymerization between the diiodide **9** and the

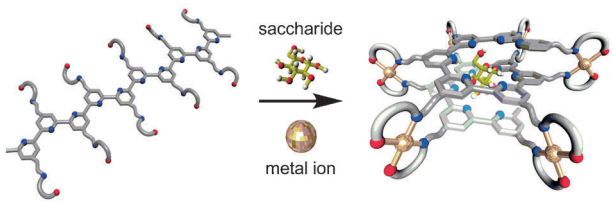

Fig. 2 Schematic diagram of helix stabilization of *meta*-ethynylpyridine host polymers by coordination of metal ions at the side chains.

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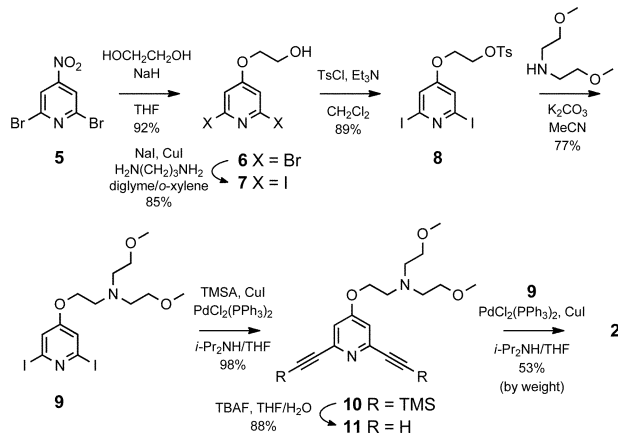
† Electronic supplementary information (ESI) available: Detailed synthetic procedures for **2–4**, Fig. S1–S5. The corresponding UV changes are shown in Fig. S6–S10. See DOI: 10.1039/c1cc12358k



Scheme 1 Preparation of host polymer **2**. TMSA = trimethylsilylacetylene, TBAF = tetrabutylammonium fluoride.

diacetylene **11** was carried out by the Sonogashira reaction to yield the polymeric product **2** as a brown oil. After the treatment with a short Sephadex LH-20 column, the product was subjected to gel permeation chromatography (GPC), and one fraction of M_n = 12 700 g mol^{-1} (*vs.* polystyrene (PS) standards) was applied to the following experiments. The polymers **3** and **4**, in which Cu(II)-coordination sites are attached through longer spacers than that of **2**, were prepared by similar procedures by using diethylene glycol and triethylene glycol instead of ethylene glycol, respectively (see ESI†). After GPC separation, each fraction of **3** (M_n = 12 500 g mol^{-1} *vs.* PS standards) and **4** (M_n = 16 200 g mol^{-1} *vs.* PS standards) was used. These M_n values for the fractions of **2**, **3**, and **4** correspond to *ca.* 46-, 39-, and 45-meric pyridylene ethynylene polymers, respectively.

Saccharide recognition ability and additive effects of a Cu(II) ion were studied on the basis of CD spectra. The applied glycoside guests in this study were octyl β-D-glucopyranoside (**β-D-Glc**), octyl β-L-glucopyranoside (**β-L-Glc**), octyl β-D-fructopyranoside (**β-D-Fru**), and octyl β-D-mannopyranoside (**β-D-Man**) (Fig. S1 in ESI†). When **β-D-Glc** was added to a CH_2Cl_2 solution of **2** (1.0 mM, unit conc.), a negative ICD band appeared around CD_{max} = 336 nm (Fig. 3, red solid line).[11] This observation is indicative of the formation of the helical complex between **2** and **β-D-Glc**. The shape of the ICD was similar to those observed in the cases of other kinds of *meta*-ethynylpyridine polymers associated with **β-D-Glc**.[4] When Cu(II) triflate (0.5 mM, 0.5 eq. to pyridine units of **2**) was added to this mixture, the ICD was remarkably enhanced and CD_{max} slightly shifted to 343 nm (Fig. 3, green solid line). Subsequent addition of ethylenediamine (0.5 mM) in order to capture the Cu(II) ion weakened the ICD near to silent (Fig. 3, purple solid line).[12] These transformations of the ICD suggest that the chiral helical structure of the complex of **2** with **β-D-Glc** would be stabilized by the addition of a Cu(II) ion, and then destabilized by the addition of ethylenediamine. The reason for the destabilization may be that ethylenediamines can behave as not only Cu(II) chelating reagents but also competitive guest molecules to **2**. The opposite enantiomer guest **β-L-Glc** was subjected to the same experiments and induced a mirror-image ICD corresponding to that in the case of **β-D-Glc** (Fig. 3, broken lines). Thus, the chirality of the

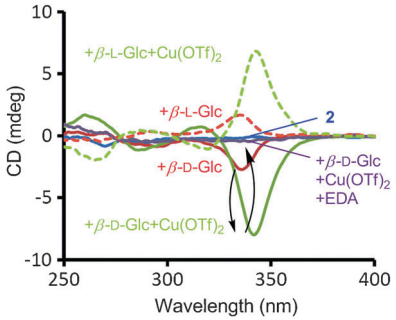


Fig. 3 The additive effect of Cu(II) triflate and ethylenediamine (EDA) on the ICDs of host polymer **2** associated with octyl β-glucopyranosides (**β-D-Glc** and **β-L-Glc**). Blue solid: **2**; red solid: **2** + **β-D-Glc**; green solid: **2** + **β-D-Glc** + $Cu(OTf)_2$; purple solid: **2** + **β-D-Glc** + $Cu(OTf)_2$ + EDA; red broken: **2** + **β-L-Glc**; green broken: **2** + **β-L-Glc** + $Cu(OTf)_2$. Conditions: **2** (1.0×10^{-3} M, unit conc.), **β-Glc** (2.0×10^{-3} M), $Cu(OTf)_2$ (5.0×10^{-4} M), EDA (5.0×10^{-4} M), CH_2Cl_2, 25 °C, path length = 1 mm. $Cu(OTf)_2$ was added as a DMSO solution of a 1/300 amount to the sample solution.

glucoside guests was found to be transferred to the helical sense of the polymer.

Other kinds of glycoside guests were also investigated under the same conditions. When applying **β-D-Fru** and **β-D-Man** to **2**, positive ICD bands appeared around 338 nm and 337 nm, respectively (red solid lines in Fig. 4A and B), almost similar to those of our previous butyloxy-substituted *meta*-ethynylpyridine polymers.[4a] However, after addition of Cu(II) triflate to the mixture of **2** and **β-D-Fru**, the sign of the ICD inverted and the absolute value largely increased (Fig. 4A, green solid line). On the other hand, slight decrease of the ICD was observed after the addition in the case of **β-D-Man** (Fig. 4B, green solid line). These transformations of the CD spectra upon the addition of a Cu(II) ion proceeded in different manners as in **β-D-Glc**. The Cu(II) ion stabilized the helical complex between **2** and **β-D-Fru** in an inverse manner of the chirality, while the complex of **β-D-Man** was scarcely affected. Indeed, ethylenediamine canceled the Cu(II) effect for **β-D-Fru** and had little influence on that for **β-D-Man**.

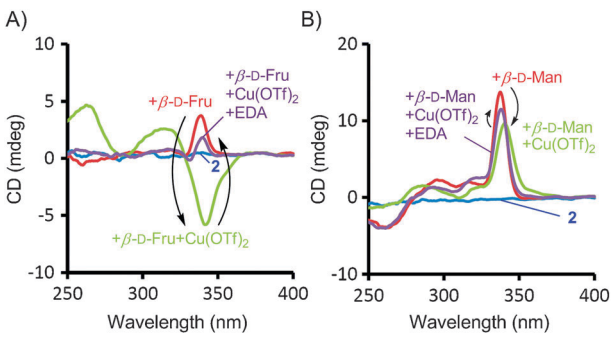


Fig. 4 The additive effect of Cu(II) triflate and ethylenediamine (EDA) on the ICDs of host polymer **2** associated with (A) octyl β-D-fructopyranoside (**β-D-Fru**) and (B) octyl β-D-mannopyranoside (**β-D-Man**). Blue: **2**; red: **2** + glycoside; green: **2** + glycoside + $Cu(OTf)_2$; purple: **2** + glycoside + $Cu(OTf)_2$ + EDA. Conditions: **2** (1.0×10^{-3} M, unit conc.), glycoside (2.0×10^{-3} M), $Cu(OTf)_2$ (5.0×10^{-4} M), EDA (5.0×10^{-4} M), CH_2Cl_2, 25 °C, path length = 1 mm. $Cu(OTf)_2$ was added as a DMSO solution of a 1/300 amount to the sample solution.

The distance between the coordination sites and the pyridine main chains proved to be important for the Cu(II)-regulated helical transformations by using **3** and **4** as a host polymer. Upon the addition of **β-D-Glc** to CH_2Cl_2 solutions of **3** and **4**, negative ICD bands were induced around 338 nm in both cases as well as in **2** (red solid lines in Fig. S2A and S2B, ESI†). However, unlike **2**, the addition of Cu(II) triflate decreased those ICDs (green solid lines in Fig. S2A and S2B, ESI†). Similar CD-decreasing effects with Cu(II) were also observed when **β-D-Fru** and **β-D-Man** were used as a guest (Fig. S3 and S4, ESI†). These observations might mean the increased freedom of the longer coordination sites, forming Cu(II) chelation with any of other sites. After those, the treatment with ethylenediamine to the mixture almost quenched the ICDs (Fig. S2–S4, ESI†).

The additive effects of the Cu(II) ion should also be ruminated from a different point of view. In the host polymers, the amino groups of the side chains and the pyridine nitrogens in the main chain can coordinate with the Cu(II) ion. In the guest glycosides, 1,2- and 1,3-diol structures can do as well.[7] The Cu(II)-induced ICD enhancement in **β-D-Glc** would reflect the stabilization of the chiral helical complex as mentioned above. This stabilization is likely to be rationalized by the following two possibilities of outside and inside coordinations: (i) one Cu(II) ion may link the two side chains outside the helix; (ii) one Cu(II) ion may link the one or two pyridine nitrogens inside the helix and one diol group of the incorporated guest glycosides. Generally, the order of coordination affinity to the Cu(II) ion will be in the following order: ethylenediamine > bis(2-methoxyethyl)amine group > pyridine ring > diol.[13] Therefore, the possibility of (i) may be plausible, and the chirality of the stabilized helix would be induced by the glycoside guest which is hydrogen-bonded inside the helix. The coordinating ability of the side chains was supported by an ^{1}H NMR experiment using **9** and $Cu(OTf)_2$ (see Fig. S5, ESI†). In the case of **β-D-Fru**, the Cu(II)-stabilized helix was inversely biased, compared to the helix without the Cu(II) coordinations (Fig. 4A).

In summary, we have prepared *meta*-ethynylpyridine polymers that possess Cu(II)-coordination sites at each pyridine unit. These polymers associate with saccharide guests and form biased helical complexes to show characteristic ICDs. The ICDs were enhanced, decreased, or inverted by the addition of a Cu(II) ion to the complex of polymer and saccharide, suggesting that the helical complex was stabilized or destabilized by cross-linking the side chains with the Cu(II) ion.

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11 See also Fig. S11 in ESI† for the titration curve.

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