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Development of convergent synthetic method for saccharide-linked ethynylpyridine foldamers by Huisgen reaction

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ABSTRACT

Based on 'click chemistry', the new convergent synthesis to a variety of saccharide-linked 2,6-pyridylene ethynylene 'ethynylpyridine' foldamers was developed. Ethynylpyridine 6-, 9-, and 12-meric blocks were linked with 1,7-octadiyne linker block by Sonogashira reaction, and joined with azido group-introduced glucoside, galactoside, and mannoside templates by Huisgen reaction. The resulting saccharide-linked ethynylpyridine foldamers exhibited typical circular dichroism to indicate the formation of a helical structure by intramolecular hydrogen bonds.

1. Introduction

Chiral helical structures are commonly seen in natural biopolymers, such as nucleic acids and proteins. On the other hand, the chemistry of chiral helical synthetic foldamers have been developed in these decades,[1] and some of them have been utilized in molecular recognition for guest species with interesting chiroptical properties.[2,3] Such functionalities are affected by the secondary structure of a foldamer, therefore, it is attractive subject to regulate the helical structures of synthetic foldamers. There have been a number of foldamers whose structure is regulated by covalently attaching a chiral template at the terminus of the foldamer.[1,4] In the course of our study of 2,6-pyridylene ethynylene 'ethynylpyridine' foldamers,[5,6] saccharide-linked ethynylpyridine oligomers have been investigated (Fig. 1).[5] These oligomers consisted of a hexose template and an oligomeric ethynylpyridine moieties, which are linked each other through an alkylene linker. Showing strong circular dichroism (CD) bands in the absorption wavelength range of the ethynylpyridine moiety, they formed chiral helical structures by intramolecular hydrogen bonds more efficiently than the cases of intermolecular association.[5] Though the effective helix formation was realized in that study, the synthetic procedures for the saccharide-linked oligomers were sequential and time-consuming. For promoting the chemistry of ethynylpyridine foldamers, it has been desired to develop the more general and convergent approach to link ethynylpyridines with regulating templates. So we decided to develop a convergent labor-saving procedure, which will open a general and comprehensive route to a variety of chiral template-linked ethynylpyridine foldamers by use of Sonogashira[7] and Huisgen[8] reactions as shown in Scheme 1.

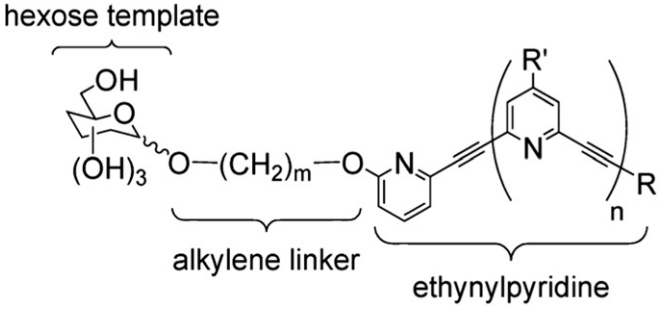

Fig. 1. Saccharide-linked ethynylpyridine oligomer in our previous work.

In Scheme 1, three types of building blocks were supposed to be essential. The first is an ethynylpyridine moiety, the second is a diyne linker, and the third is an azido group-introduced saccharide template moiety. These three blocks were assembled to yield

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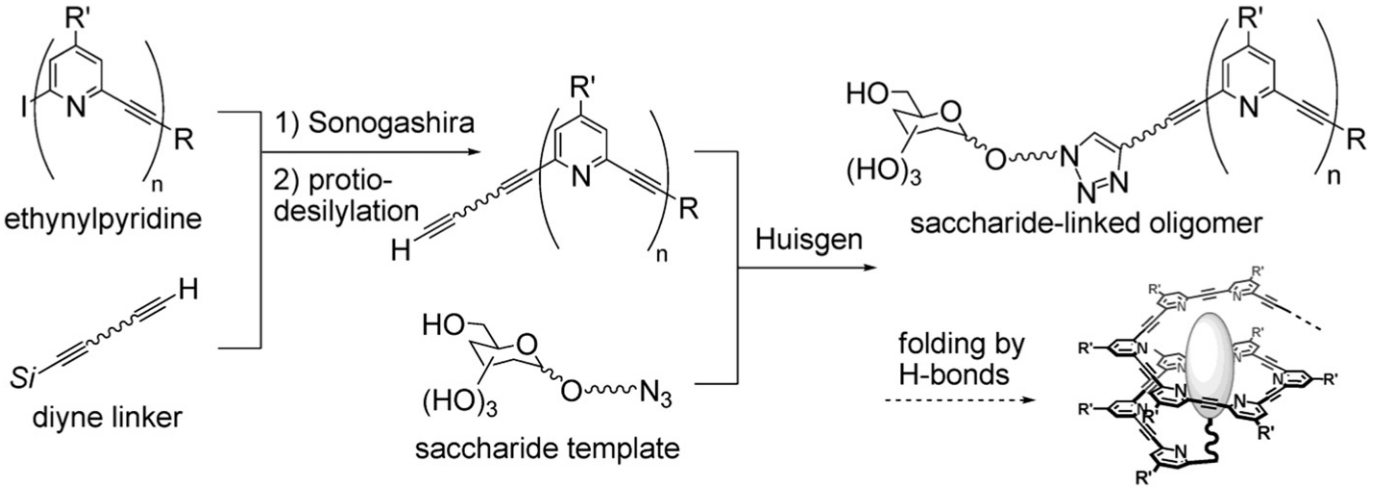

Scheme 1. Convergent approach to saccharide-linked ethynylpyridine foldamers.

a saccharide-linked ethynylpyridine oligomer, which is expected to form a helix by intramolecular hydrogen bonding between the ethynylpyridine and the template moieties. The saccharide template can be changed to another kind of saccharides and even to other chiral entities.

2. Results and discussion

Scheme 2 shows the preparation of hexameric, nonameric, and dodecameric ethynylpyridine blocks. Starting from 2,6-dibromo-4-nitropyridine,[9] 2,6-diethynyl-4-octyloxypyridine (**1**)[6c] and 2,6-diiodo-4-octyloxypyridine (**2**)[6c] were prepared by reported procedures. Sonogashira reaction using diyne **1** with excess amount of diiodide **2** gave trimeric diiodide **3**, which was converted to dissymmetrically diprotected trimeric diyne **5** via two steps of Sonogashira reactions with 2-methyl-3-butyn-2-ol and *tert*-butyldimethylsilylacetylene (TBSA) subsequently. Deprotection of the *tert*-butyldimethylsilyl (TBS) group gave **6**, and it was coupled with diiodide **3** to afford the hexameric block **7**. Nonameric block **10** was similarly prepared from hexameric block **9** and trimeric diiodide **3**. Dodecameric block **14** was prepared by assembling hexameric **7**, trimeric diiodide **3**, and trimeric diprotected diyne **5**.

1-(Trimethylsilyl)-1,7-octadiyne (**15**) as a diyne linker block (Fig. 2) was prepared from 1,7-octadiyne by the procedure in the literature.[10] To prepare azido group-introduced hexose blocks, the corresponding hexose pentaacetate[11] was condensed with 2-bromoethanol in the presence of $BF_3 \cdot OEt_2$,[11] and the resulting 2-bromoethyl glycoside tetraacetate was reacted with NaN_3[12] to give 2-azidoethyl glycoside tetraacetate, which was deacetylated.[13] β-D-Glucopyranoside **β-Glc-N$_3$**,[14] β-D-galactopyranoside **β-Gal-N$_3$**,[15] and α-D-mannopyranoside **α-Man-N$_3$**[16] (Fig. 2) were prepared and used in this study.

The assembling of three building blocks proceeded as shown in Scheme 3. First the linker block **15** and the ethynylpyridine blocks **7**, **10**, and **14** were tethered by Sonogashira reaction followed by protiodesilylation, and the resulting **19**, **20**, and **21** were subjected to Huisgen reaction with the azido group of **β-Glc-N$_3$**, **β-Gal-N$_3$**, and **α-Man-N$_3$** in the presence of $CuSO_4$ and sodium ascorbate. Table 1 shows the yields of the Huisgen reaction, and the products were identified by NMR and ESI-TOF MS analyses. The 3×3=9 kinds of saccharide-linked oligomers could be obtained from three alkynes and three azides. For the cases of 12-mers **β-Glc-12**, **β-Gal-12**, and **α-Man-12**, significant broadening of ^{1}H NMR signals was observed (see Supplementary data), suggesting the intermolecular aggregation. The chemical shift of ^{1}H NMR signal of 5-H of the triazole ring was found to be affected by the stereochemistry of the linked template. For β-glucose- and β-galactose-linked foldamers, ^{1}H NMR signals for 5-H of the triazole ring appeared downfield (δ 7.89–7.93), compared to those for α-mannose-linked foldamers (δ 7.46–7.47). From the study using CPK models, 2-OH groups of the β-glucoside and β-galactoside templates are accessible to 5-H of the triazole ring to interact,[17] while that of the α-mannoside template are not.

The generality of the convergent procedure was demonstrated by linking an amino acid moiety and two kinds of disaccharide moieties as shown in Scheme 4. Azido-derivatized amino acid **22**[18] could be linked with hexameric **19**, and the expected product **23** was obtained in good yield. Similarly, 2-azidoethyl β-lactoside and β-cellobioside (**24**[14,19] and **26**[14]) could be linked with dodecameric **21** to give products **25** and **27**, respectively.

CD and UV–vis spectra of the synthesized ethynylpyridine oligomers were measured in CH_2Cl_2 solutions (Fig. 3 and Fig. S1 in Supplementary data). Achiral oligomers **19** and **20** before the Huisgen reaction gave no meaningful CD signals. For mannose-linked hexamer **α-Man-6**, a positive CD band was induced around 320–340 nm (Fig. 3, left). The shape of this CD band was typical for helical complexes of ethynylpyridine polymer/oligomer associated with a saccharide guest,[5,6] therefore **α-Man-6** was indicated to form a helical structure as shown in Scheme 1. The mannose-linked oligomers of longer length **α-Man-9** and **α-Man-12** also showed positive CD bands around 320–335 nm. When the pyridine unit concentrations were set to 5.0×10^{-4} M, the nonameric oligomer **α-Man-9** showed the strongest Cotton effect at CD_{max}=334 nm among the saccharide-linked foldamers prepared in this study. Probably, the size of the helical pore formed inside the helix would fit with the size of the mannose template so that chiral transfer occurred efficiently. Moreover, α-glycoside bond between the mannose and the linker might bring the template to preferable location. On the other hand, glucose-linked oligomers **β-Glc-6**, **β-Glc-9**, and **β-Glc-12**, and galactose-linked oligomers **β-Gal-6**, **β-Gal-9**, and **β-Gal-12** gave smaller CD bands around 320–340 nm (Fig. 3, right). Among these cases for β-glycosides, 12-meric **β-Glc-12** and **β-Gal-12** gave the strongest negative and positive CD bands, respectively. The different length-dependency between α-glycosides and β-glycosides has been observed in the previous study of saccharide-linked ethynylpyridine oligomers (Fig. 1).[5]

Disaccharide-linked oligomers **25** and **27** exhibited CD bands as shown in Fig. 4. The intensity of CD_{max} at 327 nm for cellobioside **27** was approximately twice for that of CD_{max} at 332 nm for glucoside **β-Glc-12**. On the other hand, lactoside **25** showed much weak CD