Special Collection

A Pyridine-Acetylene-Aniline Oligomer: Saccharide Recognition and Influence of this Recognition Array on the Activity as Acylation Catalyst

Yuki Ohishi,*[a] Toshikazu Takata,[b] and Masahiko Inouye*[a]

In order to create new functions of foldamer-type hosts, various kinds of recognition arrays are expected to be developed. Here, a pyridine-acetylene-aniline unit is presented as a new class of a saccharide recognition array. The conformational stabilities of this array were analyzed by DFT calculation, and suggested that a pyridine-acetylene-aniline oligomer tends to form a helical structure. An oligomer of this array was synthesized, and its association for octyl β-D-glucopyranoside was confirmed by ^{1}H NMR measurements. UV/Vis, circular dichroism, and fluorescence titration experiments revealed its high affinity for octyl glycosides in apolar solvents ($K_a = 10^4$ to 10^5 M^{-1}). This oligomer was relatively stable under basic conditions, and therefore this array was expected to be applied to the derivatization of saccharides. A 4-(dialkylamino)pyridine attached pyridine-acetylene-aniline oligomer proved to catalyze the acylation of the octyl glucoside.

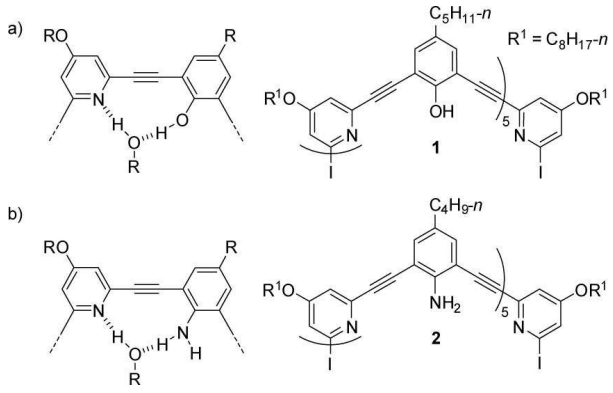

Figure 1. a) A pyridine-acetylene-phenol oligomer **1**. b) A pyridine-acetylene-aniline oligomer **2**.

Saccharide recognition is a challenging topic in the field of host-guest chemistry due to the three-dimensional complexity of saccharide structures.[1] Various types of artificial hosts have been studied for saccharide recognition. Among these studies, much interest has been focused on helical-foldamer type hosts.[2] The design using helical foldamers is rational for efficiently forming a hydrogen-bonding network with multiple hydroxy groups of saccharides. In addition, their affinity and selectivity can be regulated by modifying the recognition array in the foldamers. In order to create new functions of foldamer-type hosts, various kinds of recognition arrays are expected to be developed.

Recently, we have developed oligomers consisting of pyridine-acetylene-phenol units as hosts for saccharides (Figure 1a).[3] The pyridine and phenol rings can work as a hydrogen-bonding acceptor and donor, respectively, in a push-pull fashion for the saccharide hydroxy groups.[4] For example, chain-type oligomers, such as **1**, strongly associated with saccharides to form helical complexes in apolar solvents.[3f] During the course of this study, we imagined that a pyridine-acetylene-aniline unit could also show effective hydrogen-bonding ability (Figure 1b).[5] Since amino groups of the aniline rings can work as a hydrogen-bonding donor, this unit was expected to form a push-pull hydrogen-bonding with saccharide hydroxy groups. To apply this unit for saccharide recognition, we newly synthesized a pyridine-acetylene-aniline oligomer **2**. DFT calculations proposed that a model oligomer of **2** winds around methyl β-D-glucopyranoside by forming a hydrogen-bonding network (Figure 2). From another perspective, this recognition array seemed not to be influenced by basic conditions, usually used in acylation of saccharides, because pyridine and aniline rings have no acidic proton unlike a phenol ring. Therefore, this unit was expected to be applied to catalysts for derivatization of saccharides. Catalysts bearing saccharide-recognition arrays are expected to catalyze regioselective derivatization of saccharides like natural enzymes.[6–8] For example, Kawabata and coworkers reported successful examples of regioselective acylation for monosaccharides with a 4-(dimethylamino)pyridine (DMAP)-based catalyst bearing hydrogen-bonding sites with saccharides.[8c,e] Herein, we report saccharide recognition abilities of a pyridine-acetylene-aniline oligomer **2** and catalytic abilities of a DMAP-attached oligomer **3** (Figure 3).

Generally, helix-forming ability of *m*-aryleneethynylene foldamers is affected by the difference between cisoid- and

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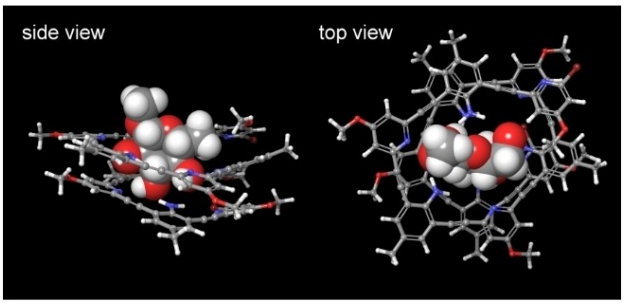


Figure 2. An example of the complex structure between **2′** and methyl β-D-glucoside. The model **2′** is an analogue of **2**, where terminal iodine atoms are changed to bromine atoms and side alkyl chains are shortened to methyl groups. An initial geometry of the complex was obtained from MacroModel-based Monte Carlo simulation (OPLS3e, under vacuum, from 30,000 conformations), and the geometry was re-optimized by DFT calculation at M06-2X/6-31G(d) level of theory under vacuum. This conformation just represents one of dynamically changing host-guest complex conformations.

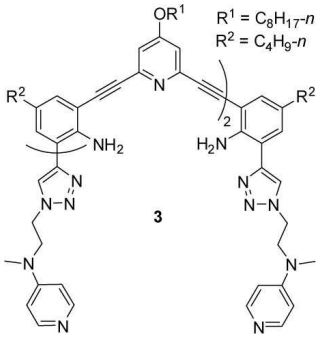


Figure 3. A DMAP-attached pyridine-acetylene-aniline oligomer **3**.

transoid-conformation stabilities of their constituent units.[9] Cisoid conformation is needed for the foldamers to form helical structures. First, we studied conformation stabilities of the pyridine-acetylene-aniline unit by DFT calculation. The conformation stabilities were estimated by using a model compound **Pyr**–**Ani** (Figure 4). The cisoid conformer proved to be more stable than the transoid one by 1.49 kJ mol^{-1}. The superiority of cisoid conformation can be rationalized by the repulsion of

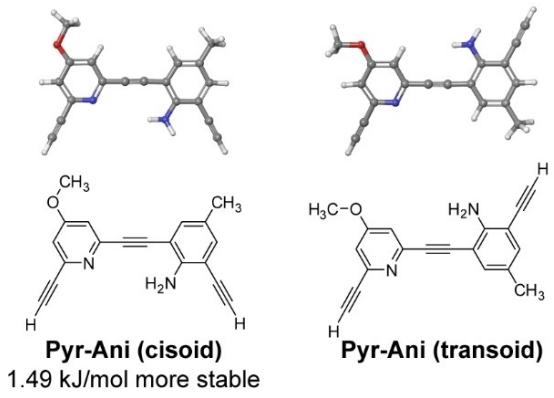


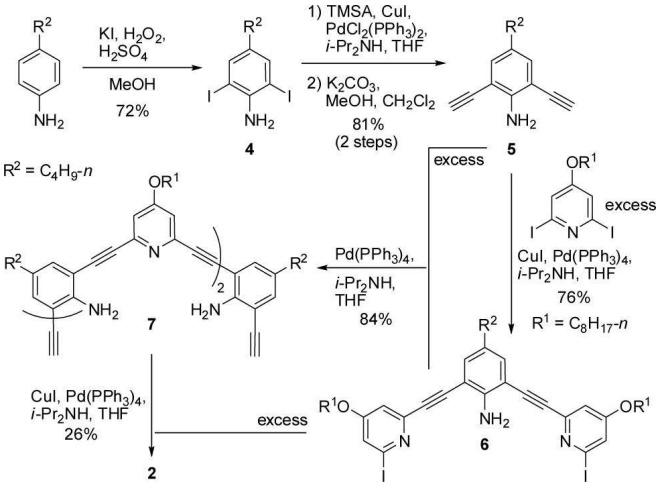
Figure 4. Calculated stability of cisoid and transoid conformers of **Pyr**–**Ani**. The geometry was optimized by DFT calculation at M06-2X/6-311 + G(d,2p) level of theory in $CHCl_3$ (CPCM).

dipole moments between the pyridine and aniline rings (Figure S1 in the Supporting Information). This finding suggests that a pyridine-acetylene-aniline oligomer tends to form a helical structure.

Scheme 1 shows the synthetic procedure of **2**. Iodination of 4-butylaniline gave **4**, which was converted to **5** by Sonogashira reaction with trimethylsilylacetylene followed by protodesilylation. The oligomer **2** was synthesized by repeating Sonogashira reactions from the aniline derivative **5** and 2,6-diiodo-4-octyloxy-pyridine.[10] On the other hand, a pyridine-acetylene-phenol reference **1** was synthesized in a similar way (Scheme S1).

We compared ^{1}H NMR spectra of oligomer **2** and its precursors **6** and **7** to study the higher-order structures of the oligomer. Aromatic proton signals of **2** were observed at higher magnetic fields relative to those of the precursors (Figure S2). This difference from the precursors probably results from spontaneous helix formation of **2**. Similar length-dependence has been reported for other oligo(arylene ethynylene)s to form helical higher-order structures.[9a] Spontaneous helix formation of **2** can be interpreted to result from that the cisoid conformation of pyridine-acetylene-aniline units is more stable than the transoid one.

^{1}H NMR analyses were performed to get the evidence of the complex formation between **2** and octyl β-D-glucopyranoside (**oct-Glc**, Figure 5). The spectrum of a mixed solution of **2** and **oct-Glc** was compared to each individual ^{1}H NMR spectrum of **2** and **oct-Glc** in $CDCl_3$ (Figure 6). The signals of N–H protons in **2** shifted downfield by mixing with **oct-Glc**. This downfield shift was probably caused by intermolecular hydrogen-bonding with hydroxy groups in **oct-Glc**. The axial C–H proton signals of **oct-Glc** also moved downfield by mixing. These changes most likely



Scheme 1. Synthesis of an oligomer **2**. TMSA = trimethylsilylacetylene.

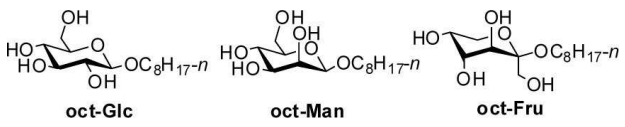


Figure 5. Structures of guest glycosides

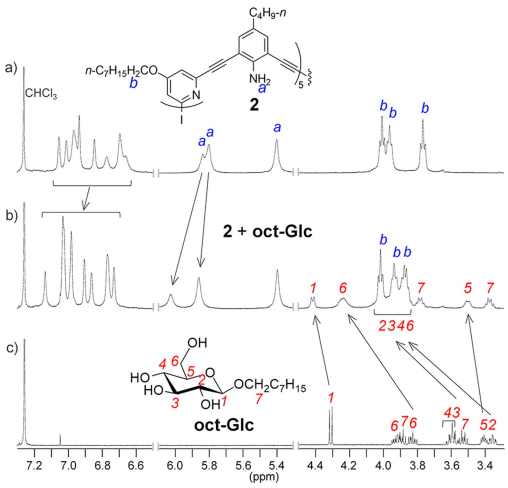


Figure 6. ^{1}H NMR spectra of a) **2**, b) **2** and **oct-Glc**, and c) **oct-Glc**. Each signal of **oct-Glc** was assigned by the ^{1}H NMR spectra of the solutions of **2** and **oct-Glc** in a ratio of 1:2, 1:3, and 1:4 (Figure S3). Conditions: [**2**] = [**oct-Glc**] = 2.0×10^{-3} M, $CDCl_3$, 25 °C, 500 MHz.

Table 1. Association constants with glycosides.

Host	Guest	K_{11} [M^{-1}] UV/vis	CD	Fluorescence
2[a]	**oct-Glc**	4.9×10^4	3.1×10^5	4.6×10^4
2[a]	**oct-Man**	7.1×10^4	9.0×10^4	3.4×10^4
2[a]	**oct-Fru**	4.3×10^4	2.3×10^5	3.9×10^4
1[b]	**oct-Glc**	5×10^7	3×10^7	3×10^7

Conditions: DCE, 25 °C. [a] The K_{11} values were obtained by UV/vis, CD, and fluorescence emission titrations (Figure 7, and S5-S7). [b] The K_{11} value was obtained by curve-fitting analyses assuming 1:1 and 2:1 complex (Figure S4).

result from the encapsulation of **oct-Glc** into the helical cavity of **2**, which would cause the axial C–H protons to be influenced by nitrogen atoms of amino groups and pyridine rings.

The titration experiments were carried out to quantitatively evaluate the saccharide recognition of **2**. A 1,2-dichloroethane (DCE) solution of **2** was titrated with **oct-Glc** while UV/Vis, circular dichroism (CD), and fluorescence emission spectra were recorded (Figure 7). The addition of **oct-Glc** caused a red-shift of absorption band around 390 nm, the induction of a negative CD band around 430 nm, and decrease in fluorescence emission of **2**. These changes suggest that **2** and **oct-Glc** formed a chiral complex. Similar changes were observed in the case of pyridine-acetylene-phenol oligomer **1** (Figure S4). The titration curves drawn from the above spectral changes were fitted with the theoretical curves assuming 1:1 association (Figure S5). The average association constant K_{11} of the three methods was determined to be 1.4×10^5 M^{-1} (Table 1). Although the affinity of **2** for **oct-Glc** is lower than that of **1** (4×10^7 M^{-1}), this value is sufficient enough for the application in catalytic reactions, which are carried out at higher concentration conditions. Titration experiments with other glycosides, octyl β-D-mannopyranoside (**oct-Man**) and fructopyranoside (**oct-Fru**), revealed that **2** shows sufficient affinity for various glycosides (Figure S6 and S7).

The difference in the affinities of **1** and **2** to **oct-Glc** was reconsidered from the view point of hydrogen-bonding strength. The interaction energies (E_{int}) of push-pull type hydrogen-bonding between model molecules, **Pyr**–**Ani** and **Pyr**–**Phe**, and MeOH were estimated by DFT calculation (Figure 8, Table S1 in the Supporting Information). The E_{int} between **Pyr**–**Ani** and MeOH was lower than that between **Pyr**–**Phe** and MeOH by 4.40 kJ mol^{-1}. The weaker hydrogen-bonding ability was considered to contribute to the lower affinity of **2**.

The stability of **1** and **2** under a basic condition was investigated in order to evaluate the usefulness as a recognition site of acylation catalysts. Temporal changes of CD spectra were recorded after the addition of triethylamine into a DCE solution of an oligomer and **oct-Glc** (Figure 9). CD intensity of **1** gradually decreased with time and disappeared after 72 h, while the half of that remained in **2**. *o*-Alkynyl phenol derivatives were known to form benzofuran rings under basic conditions.[11] For pyridine-acetylene-aniline structures, a similar decomposition to indole might occur slowly.

Finally, we synthesized DMAP-attached pyridine-acetylene-aniline oligomer **3** (Scheme S2), and studied its catalytic ability. In order to clarify that the DMAP sites linked to the oligomer exhibits catalytic activity, the catalytic activity for acylation of *i*-propanol, which is a simple secondary alcohol, was evaluated. Acylation of a secondary alcohol is known to be difficult to proceed without DMAP in comparison to that of a primary alcohol.[12] The acetylation of *i*-propanol successfully proceeded

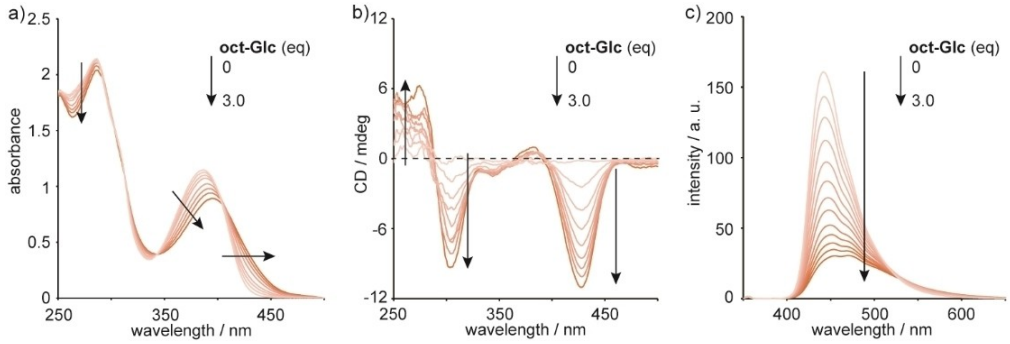


Figure 7. Results of the titration experiment of **2** with **oct-Glc**. (A) The UV/vis, (B) the CD, and (C) the fluorescence spectra. Conditions: [**2**] = 1.0×10^{-5} M, [**oct-Glc**] = 0 to 3.0×10^{-5} M, DCE, 25 °C, path length of 10 mm, λ_{ex} = 354 nm.

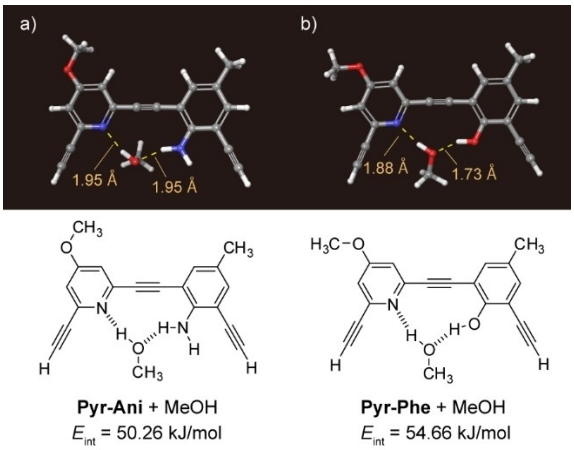


Figure 8. DFT-optimized structures of complexes between model molecules and MeOH. (a) **Pyr**–**Ani**. (b) **Pyr**–**Phe**. The geometry was optimized by DFT calculation at M06-2X/6-311+G(d,2p) level of theory under vacuum.

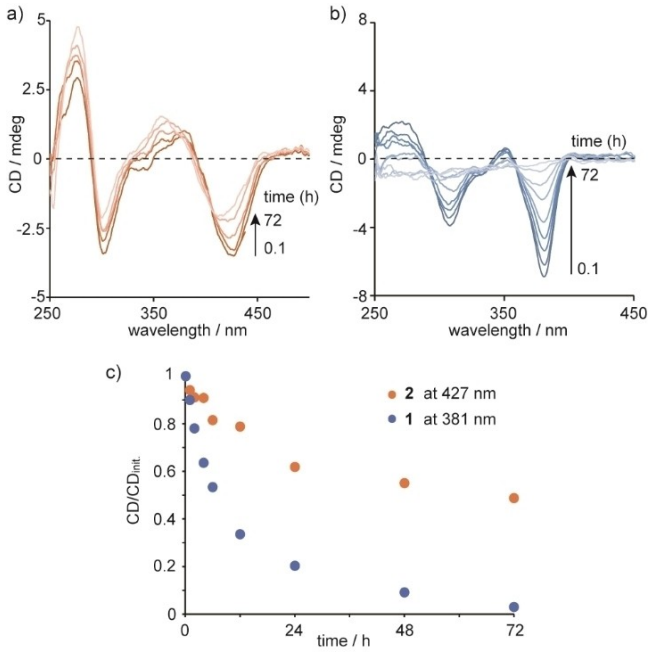
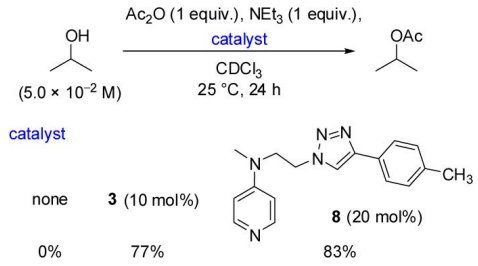


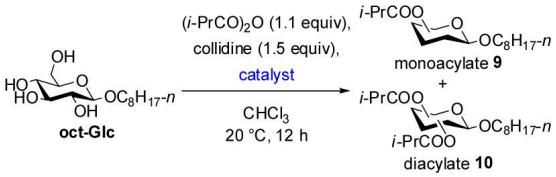
Figure 9. CD changes after the addition of triethylamine. a) **2** and **oct-Glc**. b) **1** and **oct-Glc**. c) Changes of intensities of the first CD bands. $CD_{init.}$ is the CD values at 0.1 h. Conditions: [**1**] = [**2**] = 5.0×10^{-6} M, [**oct-Glc**] = 1.5×10^{-5} M, [triethylamine] = 1.0×10^{-2} M, DCE, 25 °C, path length of 10 mm.

by using **3** as well as using reference **8** (Scheme 2). This finding means that the DMAP moieties can show catalytic activity even when linked to the pyridine-acetylene-aniline structure. Furthermore, even when the acetylation of *i*-propanol using DMAP was performed in the presence of the pyridine-acetylene-aniline molecule **6**, the acetylation of *i*-propanol was not inhibited, and decomposition of **6** was not observed (Table S2). On the other hand, a pyridine-acetylene-phenol molecule was found to inhibit DMAP-catalyzed acylation. Furthermore, the acylation of **oct-Glc** proceeded by using **3** to give acylated glucosides and recovered **3** (Table 2, entry 2). Unfortunately, significant differences in the regioselectivity were not observed compared to when DMAP or **8** was used (Table 2, entry 1 and 3).



Scheme 2. Acylation of *i*-propanol by using **3** and **8**. Yields were estimated by ^{1}H NMR analyses. [*i*-propanol] = 5.0×10^{-2} M.

Table 2. Effects of catalysts on acylation of **oct-Glc**.



Entry	Catalyst	**9** [%]	Regioselectivity[a] 6-*O*:4-*O*:3-*O*:2-*O*	**10** [%]	Recovery [%]
1	DMAP (10 mol%)	61	39:24:37:0	22	3
2	**3** (5 mol%)	61	49:22:26:3	7	14
3	**8** (10 mol%)	48	44:23:33:0	22	18

[a] Regioselectivity (%) among four monoacylates.

In conclusion, a pyridine-acetylene-aniline unit was presented as a new class of a saccharide recognition array. A oligomer of this array was more stable than a pyridine-acetylene-phenol oligomer under a basic condition. Acylation of an alcohol proceeded by using DMAP-attached pyridine-acetylene-aniline oligomer. We are now planning to create regioselective catalysts by modifying a connection fashion between the recognition array and DMAP moieties.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Acylation · DMAP · Helical Structures · Hydrogen bonds · Molecular recognition

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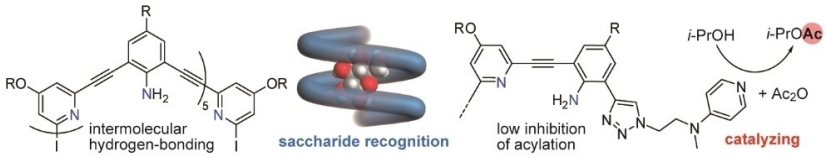
COMMUNICATIONS



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