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Alternating 2,6-/3,5-Substituted Pyridine-Acetylene Macrocycles: π-Stacking Self-Assemblies Enhanced by Intermolecular Dipole–Dipole Interaction

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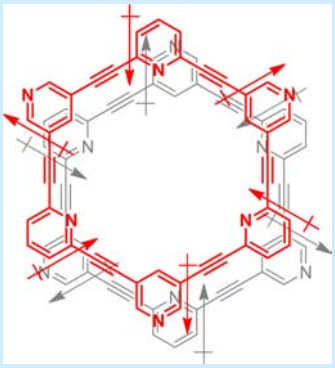
Supporting Information

ABSTRACT: Macrocyclic compounds consisting of three 2,6-pyridylene and three 3,5-pyridylene units linked by acetylene bonds were synthesized by a Sonogashira reaction. The X-ray structures showed π-stacked pairs of two macrocycles, in which a 2,6-pyridylene unit of the one molecule overlaps a 3,5-pyridylene of the other molecule because of dipole–dipole interaction. Atomic force microscope (AFM) measurements revealed fibril structures indicating the stacking of the rigid planar macrocycles. Hydrogen-bonding ability of the macrocyclic inside was demonstrated by the addition of octyl β-D-glucopyranoside.



In the design of host architecture, one of the promising strategies is to implant multiple functional groups inside a macrocyclic scaffold. The appropriate arrangement in the scaffold brings about a cooperative effect of the functional groups.[1] In addition, rigidity and symmetry of the host structures[2,3] may reduce the entropic disadvantage due to a loss of freedom during the formation of host–guest complexes or higher-order structures.

Our group has investigated *m*-ethynylpyridine polymers and oligomers as host molecules for saccharide recognition.[4−6] In this connection, we also attempted to develop (2,6-pyridylene ethynylene) cyclic hexamer **1**, an ideal rigid planar macrocycle[7] with D_{6h} symmetry. Unfortunately, so far we have failed to synthesize the target **1** because of the adverse effect of the local dipole moment at each pyridine ring.[4,8] Thus, when we tried a Sonogashira reaction at the cyclization step to obtain **1** from precursor **2**, we had to face the serious difficulty that the one end of the chain of **2** hardly approaches to the other end. Next, we aimed for another type of macrocycle **3a** involving two 1*H*-4-pyridone units (Figure 1) to avoid the disadvantage caused by the local dipole moments. However, the electron deficiency of the pyridone units prohibited a Sonogashira reaction, so that we applied oxidative dimerization by Eglinton procedure as a last resort to obtain long-hexagonal **3b** instead.[9]

To achieve a hexagonal macrocyclic structure of symmetry higher than that of **3**, we made a plan to develop the D_{3h}-symmetric structure **4** as shown in Figure 1, which involves six pyridine rings of two kinds.[10] Three of them are 4-alkoxy-2,6-pyridylene units, which we named "inward-pyridines" because

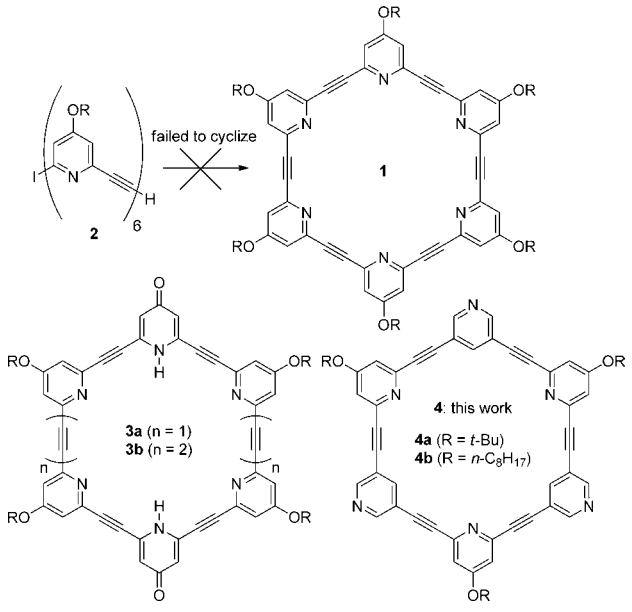


Figure 1. Macrocyclic hexagonal molecules consisting of the pyridylene ethynylene structure.

their nitrogen atoms are directed into the macrocycle, and the other three rings 3,5-pyridylene "outward-pyridines" units, of

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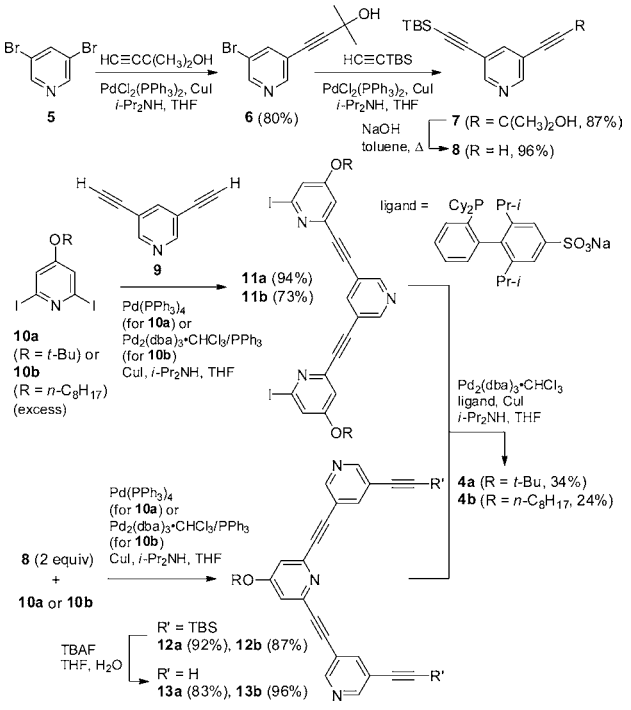
which the nitrogen atoms are directed outward. These inward- and outward-pyridine rings in **4** are arranged alternately[11] in a D_{3h}-symmetric manner. In the preparation of **4**, the cyclization step should no longer connote the disadvantage caused by local dipole moments at the pyridine units, as in the case of the previous attempt for **1**. Comparing two conformers of 1-(2-pyridyl)-2-(3-pyridyl)ethyne compound as a model of the alternating structure, we predicted that the C-shape conformer, which is favorable for the cyclization to **4**, is slightly more stable than the other one by DFT calculations (see Figure S1 in Supporting Information). Therefore it was expected that **4** could be obtained without being affected by the local dipole moments. Consequently, the alternating structure would strengthen the π-stacking self-assembly of **4** in which one inward-pyridine unit faces one outward-pyridine unit of opposite dipole direction.[12] Furthermore, the nitrogens of inward-pyridine units of **4** would work as hydrogen-bonding sites to incorporate guest molecules inside the hexagon. Herein, we present preparation of alternating macrocycles **4** and their self-assembled structures enhanced by the dipole−dipole interaction and analysis based on X-ray crystallography and atomic force microscopy (AFM).

The targeted alternating hexagonal compounds **4a,b** were prepared as in Scheme 1, using four kinds of pyridine

Scheme 1. Preparation of Hexagonal Compounds 4a and 4b[a]



[a]TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride.

derivatives, 3,5-disubstituted pyridines **8** and **9** and 4-alkoxy-2,6-diiodopyridines **10a** and **10b**, as building blocks. Monoprotected diyne **8** was prepared from 3,5-dibromopyridine (**5**) via three steps, and other blocks **9**,[13] **10a**,[14] and **10b**[5] were prepared as previously reported. Trimeric diiodide **11a** was obtained by a Sonogashira reaction of diyne **9** with an excess amount of **10a**. On the other hand, a Sonogashira reaction of **10a** with 2 equiv of **8** gave TBS-protected trimer **12a**, which was treated with TBAF to remove the TBS groups to give the corresponding product **13a** bearing two free terminal acetylene groups. The octyloxy analogues **11b** and **13b** were prepared in a similar way. The final products **4a** and **4b** could be obtained in moderate yields by tandem coupling of diiodide **11a** and diyne **13a** and that of **11b** and **13b**, respectively.[15] The appearance of these products was pale yellow to brown solids soluble in organic solvents such as $CHCl_3$, CH_2Cl_2, and THF. ^1H and ^{13}C NMR measurements of **4** showed very simple spectra indicating their highly symmetrical structures.

X-ray crystallography analyses for **4a** provided evidence not only about its molecular structure but also about its intermolecular π-stacking behavior. The shape of the π-system in **4a** was almost planar, and it was also found that **4a** formed a stacked dimer, in which one inward-pyridine unit of the one molecule overlies one outward-pyridine unit of the other molecule (Figure 2A). These stacked two macrocycles slip each

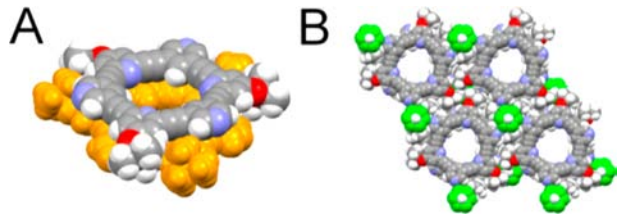


Figure 2. Single crystal X-ray structures of **4a** depicted in space-filling representation. The single crystal of **4a** was obtained from $CHCl_3$/ethyl acetate. (A) A stacked pair of **4a**. (B) Arrangement of **4a** with $CHCl_3$ viewed along the *c* axis. Two conformations observed for $CHCl_3$ are superimposed. The corresponding ball-and-stick model is shown in Figure S2 in Supporting Information.

other in a helical manner, so that the atoms are placed over bonds. The distance between the planes of the two stacked macrocycles was 3.49 Å, confirming the contribution of the π-stacking interaction. It is supposed that the stacking affinity between inward- and outward-pyridine rings would be mainly due to the local dipole moments of opposite direction on the two pyridine rings. The structure of the dimer was also characterized by the space-filling feature of the macrocycles in parallel with the *ab* plane. Three neighboring macrocycles on this plane are symmetrically located by the 3-fold rotation axis. The six *t*-BuO groups of the stacked dimer played a role in effectively filling the residual space among the macrocyclic pairs. The included chloroform molecules worked as an additional fragment in the stacking of the dimer layers on the *ab* plane along the *c*-axis to form three-dimensional structure (Figure 2B). This structural property of **4a** clearly indicates its potential to form a self-assembled network based on strong π-stacking with effective space filling.

An X-ray diffraction measurement was also carried out for a powdery solid sample of **4a** before recrystallization. The data revealed that the powdery sample is characterized by the crystallographic structure obtained on the basis of the single crystal analysis of **4a**, as shown in Figure S4 in Supporting Information. This finding also indicates a high potential of **4a** to form π-stacking self-aggregation represented in Figure 2.

We expected that **4** would form some kind of organized textures. The self-assembly of **4** was further studied by AFM. Figure 3A shows the AFM image of **4a** spread on mica. A number of fibers were observed in this image, and the fibers were substantially equal in height and width and arranged side by side. This fibril structure may be a bundle for π-stacking self-

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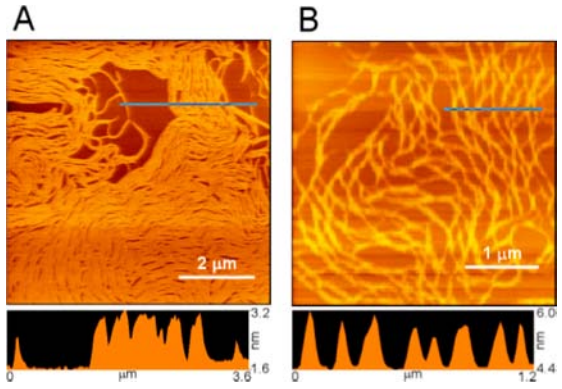

Figure 3. (Top) A non-contact mode AFM image of a self-assembled fibril structure of (A) **4a** and (B) **4b** by spreading a CH_2Cl_2 solution of **4a** (1.0×10^{-5} M) or **4b** (1.0×10^{-4} M) on a mica surface, followed by drying in vacuo. (Bottom) Line scan profile as marked in images A and B.

assembly of **4a** enhanced by dipole−dipole interaction. The higher symmetry of **4a** would cause the uniformity of the threads, as in the cases of *m*-phenylene ethynylene macrocycles investigated by Moore et al.[16] For **4b**, the AFM image displayed a similar type of fibril structure as shown in Figure 3B. Therefore, the driving force for these fibril structures should be the aggregation of the hexagonal rigid macrocycles as observed in the X-ray analyses.[17]

Saccharide recognition ability of **4b** was studied by the treatment of octyl β-D-glucopyranoside (**Glc**) as a guest. In ^{1}H NMR measurements in $CDCl_3$ (Figure S5 in Supporting Information), the chemical shifts of signals of four O*H* and one anomeric 1-C*H* protons in **Glc** moved downfield in the presence of **4b**. At the same time, among three kinds of C*H* protons on the pyridine rings of **4b**, only the one at the 4-position of 3,5-pyridylene units shifted slightly downfield in the presence of **Glc**. These C*H* protons direct inward to the macrocycle. On the other hand, the other protons, at the 2- and 6-positions of the 3,5-pyridylene units and at the 3- and 5-positions of the 2,6-pyridylene units, are directed outward from the macrocycles and their signals scarcely shifted. Thus **Glc** was incorporated within the host macrocycle, and these findings indicated that the hole of the macrocycle can work as a hydrogen-bonding recognition site. The 1:1 binding constant was estimated as $(7.5 \pm 1.2) \times 10^1$ M^{-1} from the curve-fitting analysis of the titration curve (Figure S6 in Supporting Information).

In summary, we designed and prepared D_{3h}-symmetric macrocyclic compounds **4a** and **4b** consisting of three 2,6-pyridylene and three 3,5-pyridylene units alternately linked with acetylene bonds. The three nitrogen atoms of the 2,6-pyridylene units are directed inward to the hexagon, and the other three of the 3,5-pyridylene units are directed outward. Self-assembled stacked structures and fibril higher-order structures were observed in X-ray crystallography and AFM, respectively. These π-stacked structures are enhanced by dipole−dipole interaction between the rigid and highly symmetrical macrocyclic structures. Affinity of **4b** and octyl glucoside was studied by ^{1}H NMR experiments, and it was found that the macrocycle could incorporate the glucoside by hydrogen bonding.

We are now planning to investigate the further functionalization of the macrocycles. The three nitrogen atoms of the outward-pyridine rings would be useful as binding sites to make *N*-substituted pyridinium compounds, metal−organic frameworks (MOFs), and so on.

■ ASSOCIATED CONTENT

Supporting Information

Figures S1−S6, Table S1, experimental details for the preparation of **4a**,**b**, experimental details and the CIF file for X-ray crystallography of **4a**, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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