CL-170815 Received: August 28, 2017 | Accepted: September 19, 2017 | Web Released: September 23, 2017

Preparation and Higher-order Structures of 2,6-Pyridylene and 2,6-Pyrazylene Alternating Macrocycle with the Inner Nitrogen Atoms in All the Aromatic Rings

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A shape-persistent macrocycle (SPM) consisted of three 2,6-pyridylene and three 2,6-pyrazylene rings alternately linked with acetylene bonds was prepared by Sonogashira reactions. X-ray crystallography revealed the planar macrocyclic structure, and intermolecular π-stacking was observed at the sides of the hexagon. An AFM measurement of the sample prepared by drop-casting on a mica substrate showed a reticulate fibril.

Keywords: Shape-persistent macrocycle (SPM) | Self-assembly | Sonogashira reaction

Self-assembly of π-conjugated molecules has attracted significant interest from various research fields such as supramolecular chemistry.[1] In particular, macrocyclic molecules known as shape-persistent macrocycles (SPMs) have been developed to build one-dimensional self-assembly structures.[2–5] So far, a variety of SPMs with rigid frameworks and planar π-surface have been investigated. For example, Kobayashi and co-workers developed a cyclic arylene ethynylene hexamer. In this hexamer, 2,7-anthrylene ethynylene and *meta*-phenylene ethynylene units were arranged alternately in a D_{3h}-symmetric manner.[4m] The macrocycle self-assembled by π–π interaction in $CDCl_3$ and formed nanofibers. *meta*-Phenylene ethynylene macrocycles investigated by Moore and co-workers aggregated on mica and glass to form a number of nanofibers.[4h]

In our previous reports, *meta*-ethynylpyridine polymers and oligomers have been developed, in which 2,6-pyridylene groups were linked with acetylene bonds.[6] These polymers and oligomers recognized saccharide guests by multiple hydrogen-bonding to form a helical complex. Applying this architecture to SPMs, we recently synthesized an ethynylpyridine macrocycle **1**.[5c] The macrocycle was constructed from 2,6-pyridylene and 3,5-pyridylene rings arranged alternately. Macrocycle **1** was found to self-assemble to form π-stacked molecule pairs observed by X-ray crystallography. In each pair, a 2,6-pyridylene ring of one molecule overlaps a 3,5-pyridylene ring of the other molecule, probably because of the dipole–dipole interaction between the rings of two types. Additionally, an atomic force microscopy (AFM) measurement of a sample of **1** casted on mica showed thready structures formed by self-assembly.

Next, we attempted to make ethynylpyridine macrocycle **2** that possesses a unique framework in terms of all the lone-paired electrons in nitrogen atoms being located inwardly (Figure 1). This means that all the dipole moments of the SPM convergently direct to the midpoint. The altered electric character in **2** may affect its higher-order structure by means of the dipole–dipole interaction. However, we never obtained **2** from chain precursor **3** owing to the very local dipole moment at each pyridine ring. The partial unit in **3**, a 2-pyridyl–acetylene–2-pyridyl structure, prefers transoid conformation to the cisoid one, advantageous

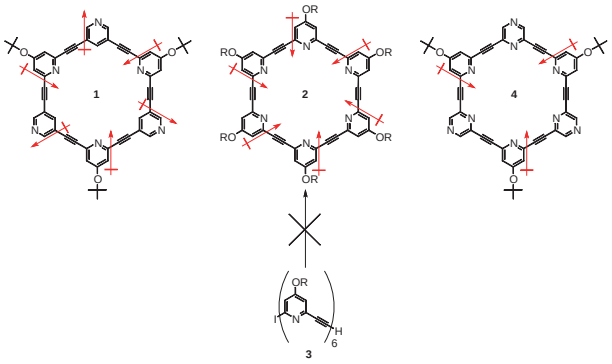
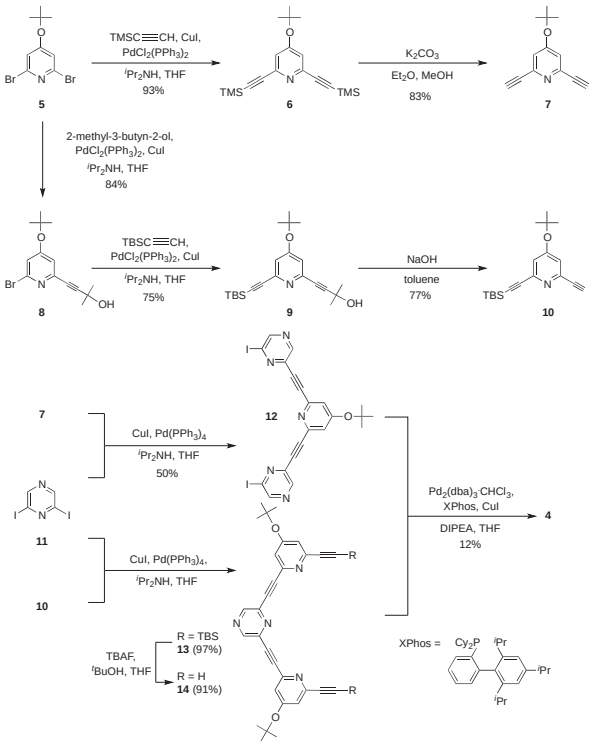


Figure 1. Macrocyclic molecules **1**, **2**, and **4** and an ethynylpyridine chain oligomer **3**.

for the cyclization because of polar repulsion. This situation largely differs from that in the precursor of **1**, i.e., the corresponding partial unit, a 2-pyridyl–acetylene–3-pyridyl structure, prefers cisoid conformation to the transoid one. Taking these findings into consideration, we planned to prepare a pyridine–pyrazine-type macrocyclic hexamer **4**. This combination may avoid at least the polar repulsion mentioned above on cyclization because of the cancelled dipole at the pyrazine rings and yet maintained the essential framework in the structure of **2**. Herein, we report the preparation of **4** and its higher-order structures by X-ray crystallography and AFM.

The targeted macrocycle **4** was prepared from two kinds of starting materials, 4-*tert*-butyloxy-2,6-dibromopyridine (**5**) and 2,6-diiodopyrazine (**11**) through sequential Sonogashira reactions, as shown in Scheme 1. Dibromide **5** was prepared from 2,6-dibromopyridine according to the procedure we reported earlier.[5a] Sonogashira reaction of **5** with two equivalents of trimethylsilylacetylene gave **6**, and the two trimethylsilyl groups of **6** were removed with K_2CO_3 in MeOH to give **7**. On the contrary, **5** was coupled with 2-methyl-3-butyn-2-ol and *tert*-butyldimethylsilylacetylene by subsequent Sonogashira reactions to yield dissymmetrically protected diyne **9**. The liberation of acetone from **9** by the treatment with NaOH gave monoprotected diyne **10**. Diiodide **11** was prepared from 2,6-dichloropyrazine by halogen exchange as reported in the literature.[7] Sonogashira reaction using **7** and an excess amount of **11** yielded trimeric diiodide **12**. Separately, coupling of **11** with two equivalents of **10** gave trimer **13**, and the two *tert*-butyldimethylsilyl groups of **13** were removed by tetrabutylammonium fluoride to give trimeric intermediate **14**. Finally, the targeted macrocycle **4** was furnished by the tandem Sonogashira coupling of the trimeric diiodide **12** with **14**. Product **4** was a colorless solid soluble in various organic solvents such as THF,



Scheme 1. Preparation of macrocycle **4**. TMS: trimethylsilyl, TBS: *tert*-butyldimethylsilyl, TBAF: tetrabutylammonium fluoride, DIPEA: *N*,*N*-diisopropylethylamine.

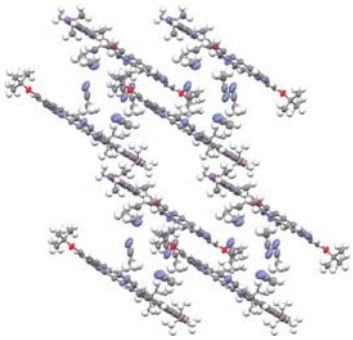


Figure 2. Crystal structure of **4**. Arrangement of **4** with CH_3CN was viewed along the *a* axis. Thermal ellipsoids were drawn at the 50% probability level.

CH_2Cl_2, and $CHCl_3$, and identified on the basis of ^{1}H NMR and ESI-TOF-HRMS measurements. ^{1}H NMR and ^{13}C NMR measurements of **4** gave simple spectra due to the symmetrical molecular structure of **4**.

Macrocycle **4** gave single crystals from the $CH_3CN/CHCl_3$ mixture. We found that solvent molecules were included in their crystals. Two of them were assigned as CH_3CN through analysis. The residual peaks were found to be disordered and then refined by using the PLATON-SQUEEZE method.[8] Consequently, the positions of C, N, and O atoms of **4** and two CH_3CN molecules could be determined with a satisfactory *R* value. As shown in Figure 2, **4** has a planar macrocycle geometry. On each of the two faces of hexagonal **4**, three other

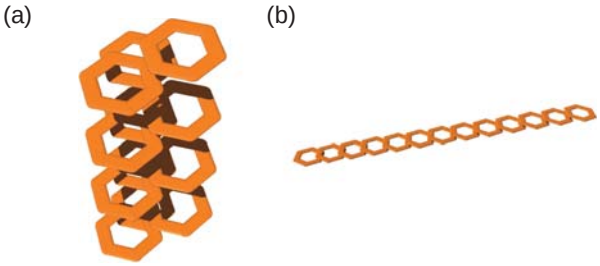


Figure 3. Schematic representation of (a) helical structure and (b) chain-like stairs in the crystal structure of **4**.

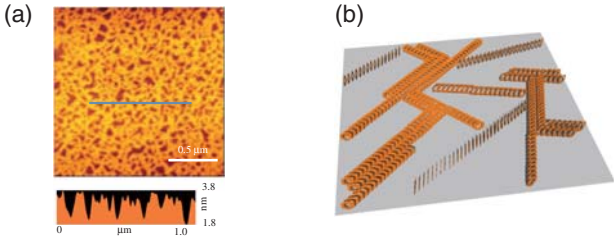


Figure 4. (a, top) An AFM image of a self-assembled fibril structure of **4** by spreading a CH_2Cl_2 solution of **4** (1.0×10^{-4} M) on a mica surface followed by drying in vacuo. (a, bottom) Line scan profile as marked in top image. (b) Schematic representation of fibril structure of **4** on mica.

molecules of **4** interact, and totally one **4** interacts with other six **4**. These interactions are π-stacking between the two pyridine–acetylene–pyrazine rims of the two hexagons, where their stacking distance was in the range of 3.331–3.397 Å. 4/1-Helical structures are observed along the direction almost normal to the $(\bar{1}\bar{2}4)$ plane, and chain-like stairs are seen along the *a*-axis (Figure 3). In the crystal structure of **1** in our previous study, a characteristic molecular dimer was constructed, in which two hexagons were fully overlapping because of the π–π interaction enhanced by dipole–dipole interaction between the reversely located pyridine rings.[5c] On the contrary, the full overlapping may give no merit to **4** since the dipole moment was totally directed inwardly. This is the reason why successive partial overlaps were found between the hexagons in **4**.

We performed AFM measurements of **4** to study its self-aggregation and higher-order structure on the surface. The sample was prepared by spreading a CH_2Cl_2 solution of **4** (1.0×10^{-4} M) on a mica substrate by drop-casting followed by drying in vacuo. A number of fibril structures were observed, as shown in Figure 4a. An AFM line-scan profile of nanofibers indicated that the height was about 2.0 nm, and this height was substantially equivalent to the size of one molecule of **4**. The hydrophilicity of the mica surface would make the hydrophobic SPM almost perpendicular against the surface. These fibril structures might be due to the self-assembly of **4** by noncovalent interaction such as π-stacking and solvophobic effect (Figure 4b).

In summary, an arylene ethynylene SPM involving three pyridine and three pyrazine units was prepared by sequential Sonogashira reactions. Its hexagonal planar structure and successive partial intermolecular interactions were assured by X-ray crystallography. The interaction mode largely differed

from that in the previously reported 2,6-pyridylene–3,5-pyridylene-type SPM because of the local dipole moments. A reticulate structure by self-aggregation was observed by an AFM measurement of a drop-casted sample.

This work was supported by JSPS KAKENHI Grand Numbers; 17H05360 and 17K05927 (HA).

We thank Dr. Makoto Gemmei-Ide (Graduate School of Science and Engineering, University of Toyama) for helpful advice on the study of self-assembly. NMR, IR, and AFM measurements were performed at Life Science Research Center, University of Toyama.

Supporting Information is available on http://dx.doi.org/10.1246/cl.170815.

This paper is dedicated to the memory of the late Professor Yoshihiko Ito, supervisor of MI.

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