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Preparation of Molecular Cage by Coordination of *m*-Calix[3]amide Bearing Pyridine with Palladium Complex

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m-Calix[3]amide having pyridine on the benzene ring (**PyC3A**) was synthesized by the cyclization of methyl 3-nonylamino-5-(pyridin-4-yl)benzoate using lithium 1,1,1,3,3,3-hexamethyldisilazide (LiHMDS). The molecular cage **3Pd·2PyC3A** was prepared from a 2:3 mixture of **PyC3A** and [Pd(dppp)(OTf)$_2$] in $CDCl_3/CD_3OD$ (5/1 in volume). On the other hand, in $CDCl_3$, the formation of a polymeric mixture was confirmed.

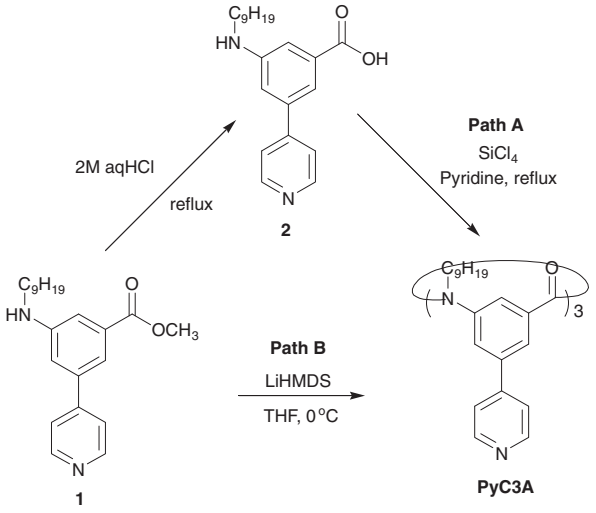
The noncovalent bond self-assembly of chemically-designed components proceeds under thermodynamic equilibrium and thus permits the generation of supramolecular cages or capsules more easily than with covalent bond approaches. The size and dimension control of supramolecular objects depends on the shape of the building blocks. Stang[1] and Fujita[2] hitherto reported many fantastic examples of self-assembled supramolecular objects using the coordination of the pyridine nitrogen to palladium complexes. They synthesized two- or three-dimensional supramolecular objects with modified building blocks. For example, ditopic building blocks with a predetermined angle gave cyclic molecules, and the combination of ditopic and tritopic building blocks afforded three-dimensional supramolecular cages. On the other hand, Shinkai and co-workers prepared molecular capsules using bowl-shaped calix[*n*]arenes as the building block through similar pyridine coordination to palladium complexes.[3–7] Molecular capsules constructed from two bowl-shaped calix[*n*]arenes provided the large cavity, which could be utilized as the host of fullerene encapsulation. In this methodology, however, the immobilization of the cone conformation by the chemical bonding was necessary for building the molecular capsules and the 1,3-alternate conformation gave uncharacterizable oligomers.

Calix[3]amide classified by Azumaya[8] is a cyclic trimer having *N*-alkylbenzanilide skeletons. In particular, calix[3]amide linked at the meta-position (*m*-calix[3]amide) likely adopts a bowl-shaped structure (vide infra). A *m*-calix[3]amide was first synthesized by Azumaya in one step using 3-alkylaminobenzoic acid as a substrate and tetrachlorosilane[9,10] or dichlorotriphenylphosphorane[8,11] as condensation reagents. On the other hand, Yokozawa investigated the cyclic trimerization of a diphenylacetylene monomer bearing 4-propylamino and 4′-methoxycarbonyl groups using lithium 1,1,1,3,3,3-hexamethyldisilazide (LiHMDS) as the base.[12] In both methods, the cyclization proceeded efficiently and cyclic trimers were obtained as the main product, owing to the *cis* preference around the amide bond of *N*-alkylbenzanilide units.[13] *m*-Calix[3]amide is known to have two conformers in solution. The *syn*-conformer has three benzene rings in the same orientation relative to the amide bond, and the *anti*-conformer has one benzene ring turning in the other direction. It is found that the preferable conformation depends on the solvent character ([*syn*]/[*anti*] = 74/26 in $CDCl_3$ and 96/4 in CD_3OD).[9]

In our previous work, *m*-calix[3]amide derivatives carrying oligothiophene chromophore on the benzene ring were synthesized and the self-assembly of a π-conjugated system influenced by the solvent character was reported.[14] Despite extensive research[8–11] on the conformation of calix[3]amides in crystal and solution states, only a minimal effort[15] has been devoted for the application as functional molecules. As mentioned above, the shape of the building block is of importance to obtain self-assembled molecular capsules. With the fact that *m*-calix[3]-amide prefers the *syn*-conformer in CH_3OH in mind, we investigated the construction of *m*-calix[3]amide-based molecular cage not by covalently fixing the conformation but by tuning the conformation with the solvent character. In this article, we will describe the synthesis and conformation analysis of a new *m*-calix[3]amide having pyridine on the benzene ring by using variable temperature (VT)-NMR, and the formation of molecular cage with palladium complexes.

3-Nonylaminobenzoic acid and its methyl ester bearing pyridine at the 5-position were prepared as monomers. Following our previous report,[14] methyl 3-bromo-5-nonylaminobenzoate was synthesized in three steps starting from 3-bromo-5-nitrobenzoic acid. The subsequent Suzuki coupling reaction with 4-pyridineboronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) afforded methyl 3-nonylamino-5-(pyridin-4-yl)benzoate (**1**) in 58% yield. The hydrolysis of methyl ester **1** under the acidic condition gave 3-nonylamino-5-(pyridin-4-yl)benzoic acid (**2**) in 68% yield.

Cyclic oligomerization was initially carried out using acid **2** based on the procedure reported by Azumaya et al. using $SiCl_4$ as the condensation reagent (Scheme 1, Path A).[9,10] The preparative GPC profile of crude products gave a multimodal curve ranging from the oligomeric region to the high-molecular-weight region (Figure S1,[18] left). The MALDI-TOF-MS also indicated the formation of macrocyclic oligomers in addition to the target cyclic trimer (Figure S2, left). In the cyclic oligomerization of 3-nonylamino-5-phenylbenzoic acid, however, the cyclic trimer could be selectively formed (not shown here). Thus the introduction of the pyridine group in the monomer structure might interrupt the effective cyclic trimerization. The cyclic oligomerization of methyl ester **1** was then performed using LiHMDS following to the method developed by Yokozawa et al. (Scheme 1, Path B).[12] In contrast to the result through Path A, the preparative GPC profile showed a good peak separation of the



Scheme 1. Cyclic oligomerization of monomers **1** and **2**.

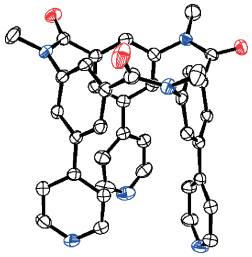


Figure 1. ORTEP view of **PyC3A′** with thermal ellipsoids drawn at 50% probability. The hydrogen atoms are omitted for clarity.

oligomeric product from the high-molecular-weight product (Figure S1,[18] right). *m*-Calix[3]amide (**PyC3A**) was successfully isolated by the preparative GPC in 16% yield. The MALDI-TOF-MS showed a signal at m/z 967.6075 assignable to the proton adduct of **PyC3A**.

Figure 1 shows the single-crystal X-ray structure of *N*-methyl analog of **PyC3A**, abbreviated hereafter as **PyC3A′**. The X-ray quality single crystals of **PyC3A′** were grown by slow evaporation in mixed solvents containing chloroform and hexane. The *syn*-conformer was observed similarly to *m*-calix[3]amide having the benzene group.[10] **PyC3A′** is obtained as a racemic crystal, in which one enantiomer has a right-handed amide skeleton and another has a left-handed amide skeleton. The X-ray data indicated an almost planar structure around the amide bond (an averaged dihedral angle Me–N–C–O was 2.3°) comparable to that of *m*-calix[3]amide having the benzene group (1.5°).[10] From the IR spectroscopic study (carbonyl stretching vibration signal) of **PyC3A** in the solid state, the dihedral angle around the amide bond might not be affected by the electron density of the π-conjugated system (bithiophene; 1650 cm^{-1}, phenyl; 1650 cm^{-1}, and pyridine; 1644 cm^{-1}).[10,14] The bowl-shaped structure of **PyC3A′** is suggested from the evidence of that the averaged distance between C(2) carbon atoms (3.78 Å) is shorter than that between pyridine nitrogen atoms (5.02 Å).

In a $CDCl_3$ solution at 293 K, ^{1}H NMR spectrum gave many signals indicating the existence of *syn*- and *anti*-conformers. The VT-NMR measurement was investigated to gain insight into the equilibrium between two conformers. **PyC3A** existed in the rapid

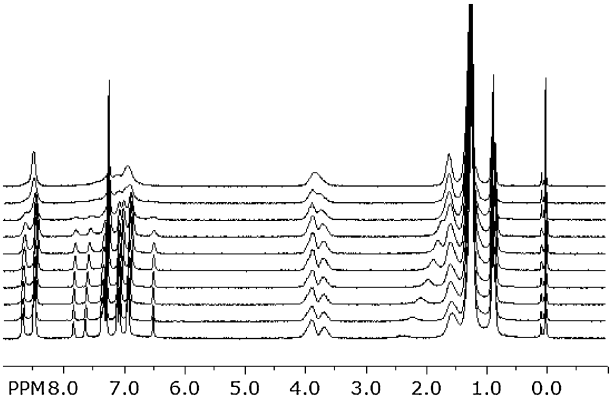


Figure 2. VT-NMR spectra of **PyC3A** in $CDCl_3$ (From top to bottom: 323–233 K with interval of 10 K).

equilibrium at above 318 ± 5 K because a pyridyl α-proton signal of the *syn*-conformer (8.46 ppm) was coalesced with that of the *anti*-conformer (8.66 ppm) (Figure 2). On the other hand, these signals were separated at below 318 K. Following the report by Azumaya et al.,[9] an observed minor signal can be assigned to a proton of the *anti*-conformer. The [*syn*]/[*anti*] ratio at 293 K was calculated from the integral ratio of these pyridyl α-proton signals to be [*syn*]/[*anti*] = 69/31 (Figure S3[18]). The [*syn*]/[*anti*] ratio was dependent on the temperature in which the *syn*-population increased with the rise of temperature ([*syn*]/[*anti*] = 70/30 at 313 K and 66/34 at 233 K). The conformation was also influenced by the solvent character. **PyC3A** existed as largely the *syn*-conformer in pure CD_3OD and the *anti*-population increased with decreasing the percentage of CD_3OD in $CDCl_3/CD_3OD$ mixed solvents (Figure S4[18]).

For the preparation of the molecular cage (**3Pd·2PyC3A**), **PyC3A** and [Pd(dppp)Cl_2] or [Pd(dppp)$(OTf)_2$] was mixed with the molar ratio of 2:3 in $CDCl_3/CD_3OD$ (5/1 in volume, 19 mM). In the ESI-MS of the mixture using [Pd(dppp)Cl_2] as the palladium complex (Figure S5[18]), no peak ascribed to the target molecular cage was detected though incomplete coordinated products were detected. Thus [Pd(dppp)Cl_2] has a poor coordination ability with pyridine due to the lack of the cationic character of palladium center. On the other hand, the ESI-MS of the 2:3 mixture of **PyC3A** and [Pd(dppp)$(OTf)_2$] showed strong peaks at m/z 2043.6100 for [**3Pd·2PyC3A** − 2OTf]$^{2+}$ and m/z 1312.4136 for [**3Pd·2PyC3A** − 3OTf]$^{3+}$ (Figure 3) indicating the formation of an ideal molecular cage (Scheme 2). In addition, the ^{31}P NMR and the diffusion-ordered NMR spectroscopy (DOSY) were investigated to confirm the efficiency of capsule formation. The phosphorous signal at 15.0 ppm for the original [Pd(dppp)$(OTf)_2$] completely disappeared and only one signal was observed at 5.21 ppm by adding [Pd(dppp)$(OTf)_2$] to a $CDCl_3/CD_3OD$ (5/1 in volume) solution of **PyC3A** (Figure S6[18]). The DOSY experiments for **PyC3A** and the 2:3 mixture of **PyC3A** and [Pd(dppp)$(OTf)_2$] showed different diffusion coefficients ($D = 5.89 \pm 0.3 \times 10^{-10}$ m^2 s^{-1} and $D = 3.74 \pm 0.6 \times 10^{-10}$ m^2 s^{-1}) (Figures S7, S8, and Table S1)[18] indicating the quantitative capsule formation. From the results, we estimated the hydrodynamic radii (R_H) by the Einstein–Stokes equation ($R_H = 0.60$ nm for **PyC3A** and $R_H = 0.96$ nm for **3Pd·2PyC3A**).[16] The increase in R_H indicated the change of molecular shape. In contrast, 2:1 mixture showed a complicated

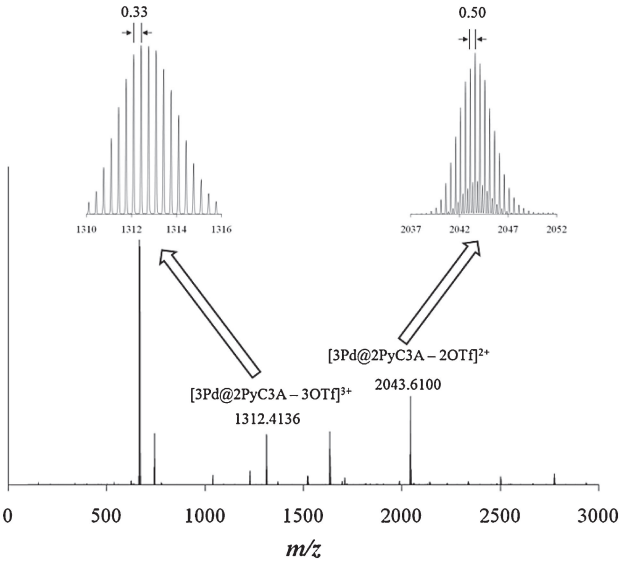
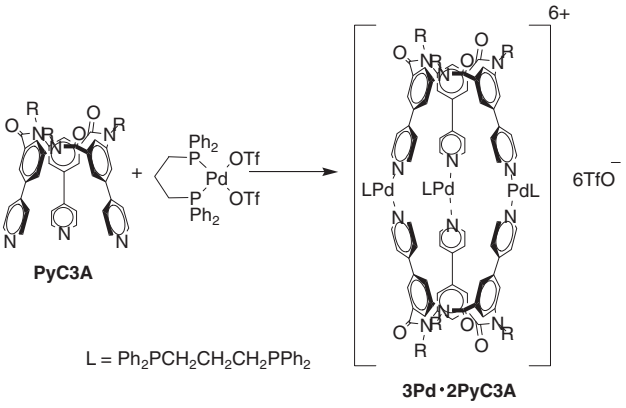


Figure 3. ESI-MS of 2:3 mixture of **PyC3A** and [Pd(dppp)(OTf)$_2$].



Scheme 2. Preparation of **3Pd·2PyC3A** from **PyC3A** and [Pd(dppp)(OTf)$_2$].

^{1}H- and ^{31}P NMR spectrum, and DOSY experiments gave several diffusion coefficients (Figures S6, S9, and S11C).[18] The ^{1}H NMR spectrum of the 2:3 mixture in $CDCl_3/CD_3OD$ (5/1 in volume) showed a new set of signals (Figure 4 and S11D[18]). The pyridyl α-proton signals at 8.43 ppm for the *syn*-conformer and 8.61 ppm for the *anti*-conformer observed in the original **PyC3A** vanished and a new proton signal was detected only at 8.90 ppm. Accordingly, *m*-calix[3]amide included in molecular cage **3Pd·2PyC3A** would be fixed as the *syn*-conformer. Finally, the solvent dependency on the cage formation was investigated. The 2:3 mixture of **PyC3A** and [Pd(dppp)(OTf)$_2$] in $CDCl_3$ gave a broad ^{1}H NMR[17] and DOSY spectra which indicated the formation of polymeric mixture (Figures S10 and S11E[18]). Two pyridyl α-proton signals (8.99 and 9.17 ppm) still remained impling the existence of both the *syn*- and *anti*-conformers. The presence of the *anti*-conformer in $CDCl_3$ may be responsible for the interruption of the effective cage formation. These findings indicate that the conformation change of **PyC3A** induced by the solvent character dramatically affects the formation of molecular cage **3Pd·2PyC3A**.

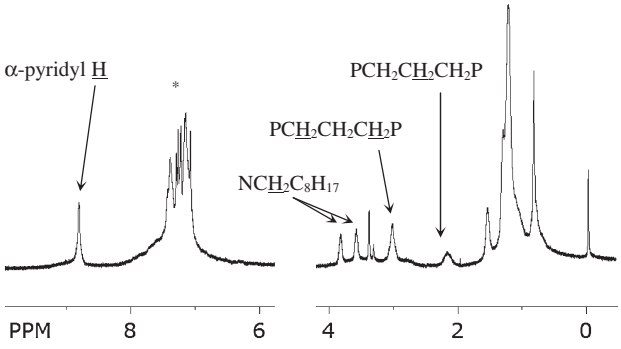


Figure 4. Expanded ^{1}H NMR spectra of **3Pd·2PyC3A** in $CDCl_3/CD_3OD$ (5/1 in volume). Some aromatic proton signals marked with asterisk were too overlapped to be assigned.

In conclusion, *m*-calix[3]amide having pyridine on the benzene ring was synthesized to obtain a molecular cage by the coordination to palladium complexes. The conformation study was carried out using ^{1}H NMR spectra to find out that *m*-calix[3]amide bearing pyridine preferred the *syn*-conformer in CD_3OD. The 2:3 mixture of **PyC3A** and [Pd(dppp)(OTf)$_2$] in $CDCl_3/CD_3OD = 5/1$ (in volume) gave molecular cage (**3Pd·2PyC3A**), which was supported by ESI-MS, DOSY, ^{1}H NMR, and ^{31}P NMR spectra. On the other hand, in $CDCl_3$, the formation of polymeric mixture was indicated. Accordingly, the conformation change of **PyC3A** triggered by solvent character has a large impact on the formation of molecular cage.

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