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Preparation of new type of azacalixarene, azacalix[*n*](2,6)pyridine

Yuko Miyazaki, Takaki Kanbara* and Takakazu Yamamoto*

Chemical Resources Laboratory, Tokyo Institute of Technology, 4259, Nagatsuta, Midori-ku, Yokohama 226-8503, Japan

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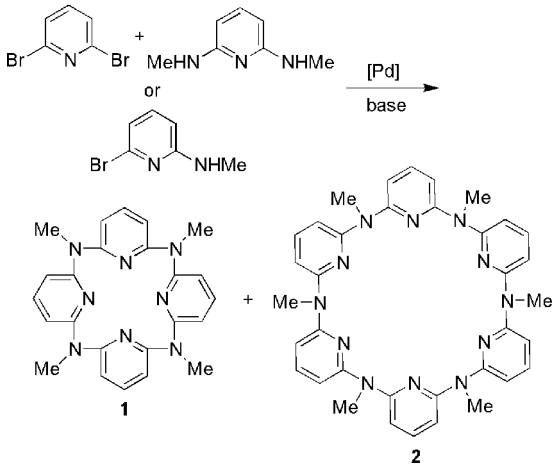
Abstract—Palladium-catalyzed aryl amination of 2,6-dibromopyridine with 2,6-bis(methylamino)pyridine or 2-bromo-6-(methylamino)pyridine gave new azacalix[*n*](2,6)pyridines ($n=4$ and 6). Molecular structure, conformation, and complexation of the macrocycles toward zinc ion were characterized by NMR spectroscopy and X-ray crystallography.

In recent years, calixarenes have attracted much attention not only due to their interesting molecular structures but also due to their forming various inclusion compounds.[1] New classes of calixarenes, in which the carbon–methylene bridge between the arylene units is replaced by heteroatoms such as silicon, nitrogen, oxygen, and sulfur, are the subject of recent interest; they have shown interesting chemical and physical properties.[2,3] Recently, catalytic aryl amination using palladium or nickel complex has widely been investigated,[4] and the aza-bridged cyclophanes have been prepared by the multiple cross-coupling reaction.[3] However, to our knowledge, preparation of azacalix[*n*](2,6)pyridine using the amination reaction has not been reported yet.

This situation prompted us to prepare novel host macrocycles, azacalix[*n*](2,6)pyridines, via the Pd-catalyzed aryl amination of 2,6-dibromopyridine with 2,6-bis(methylamino)pyridine or 2-bromo-6-(methylamino)-pyridine. Synthesis of various macrocycles containing pyridine subunits has been intensively studied in view of their coordinating and hydrogen-bonding properties,[5] because pyridine is valuable σ-donor and π-acceptor in the bonding synergism of transition-metal complexes. The introduction of pyridine unit and amine as the bridging group into the calixarenes will provide additional opportunities to tune the ring size, conformation, and binding behaviors of the macrocycles. We here report preparation of azacalix[*n*](2,6)pyridines, *N*,*N*′,*N*″,*N*‴-tetramethylazacalix[4](2,6)pyridine, **1**, and *N*,*N*′,*N*″,*N*‴,*N*⁗,*N*⁗′-hexamethylazacalix[6](2,6)pyridine, **2**, according to the Pd-catalyzed reaction; structure and preliminary coordinating properties with zinc ion of the newly prepared macrocycles are also described.



The reaction was performed under dilute conditions to minimize formation of linear oligomers. The Pd-catalyzed aryl amination of 2,6-dibromopyridine and 2,6-bis(methylamino)pyridine[6] afforded the azacalix[*n*]-(2,6)pyridines (yield: **1**, 1.5%, **2**, 10.1%), and the cyclization reaction of 2-bromo-6-(methylamino)pyridine[7] also gave the corresponding macrocycle (yield: **2**, 8.0%).[8] Although the isolated yields were not high owning to the difficulty of purification, the one-step procedure is an attractive one to synthesize

Keywords: macrocycle; amination; palladium complex; zinc complex.

* Corresponding authors. Tel.: +81-45-924-5222; fax: +81-45-924-5276; e-mail: tkanbara@res.titech.ac.jp

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such macrocycles.[9] It is interesting to note that the main product is cyclic hexamer, **2**, whereas the similar aryl amination of 3-bromo-*N*-methylaniline afforded the corresponding cyclic tetramer as the main product.[3a,b] The electrostatic repulsion between the nitrogen atoms of pyridine ring and amine in the cavity[10] seems to inhibit formation of the cyclic tetramer.

Mass spectra of **1** and **2** exhibited the molecular-ion peak of M^+ (**1**: m/z 424; **2**: m/z 636), supporting formation of the cyclic tetramer and hexamer, respectively. NMR spectra of **1** and **2** are consistent with the macrocyclic structure. In the ^{1}H NMR spectra at room temperature, sharp signals with aromatic AB_2 spin system were observed, whereas the signals were broadened at −40°C, presumably due to fluxional behavior of the macrocycles in the solution.

The crystal of **2** was obtained from slow diffusion of methanol into a $CHCl_3$ solution. Fig. 1 shows a molecular structure of **2** in the crystalline state. X-Ray structural analysis of **2** indicates that **2** adopts the absence of any symmetrical conformation with fairly distorted cavity, but the centrosymmetrical arrangement of two macrocycles in the crystallographic cell was observed.[11] The C–N–C angle of the bridging *N*-methylamine atoms between the pyridine rings is, on the average, 122°, whereas the torsion angles through the macrocyclic backbone are disparate (e.g. C30–N12–C1–N1; −16.3(1)°, C11–N4–C10–N3; −59.0(1)°). The unsymmetrical distorted conformation of **2** is also considered to be attributable to the electrostatic repulsion between the *N*-donor atoms in the cavity.[10]

The molecular structures of zinc complexes with 2,2′-dipyridylamine have been determined by X-ray crystallography,[12] and NMR spectroscopy is a valuable tool to judge the electronic effect in ligands. Since the single crystal of **1** suitable for X-ray crystallography has not been grown at present, we attempted complexation of $ZnCl_2$ with **1**. As shown in Fig. 2, addition of $ZnCl_2$ leads to downfield shifts of the ^{1}H NMR signals of **1**, which is accounted for by an assumption that coordination of zinc to **1** induces a decrease of electron density of the macrocycle.[5f] The product that crystallizes from the mixture of **1** with $ZnCl_2$ in CD_3CN is a salt with a diaqua zinc cation and a $ZnCl_4^{2-}$ anion: $[Zn^{II}\mathbf{1}(H_2O)_2][ZnCl_4]$. The molecular structure of the complex is presented in Fig. 3.[13] The zinc atom is included in the cavity of the macrocycle in a slightly elongated octahedral coordination geometry with two aqua molecules as axial ligands. The zinc metal lies in the plane determined by the four pyridine nitrogen atoms, and the O–Zn–O axis is nearly perpendicular to the plane. The complex adopts an approximate S_4 conformation in which each pyridine ring alternately

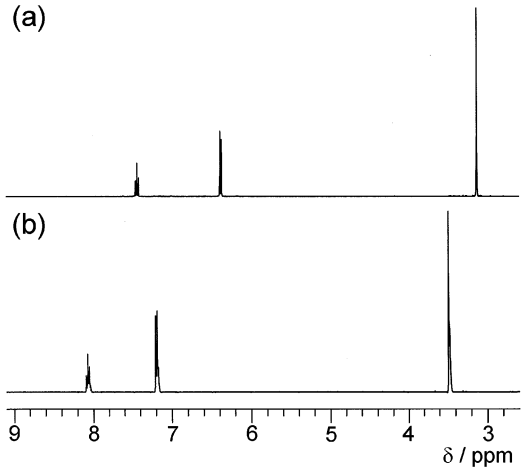

Figure 2. ^{1}H NMR spectra (400 MHz, CD_3CN, 297 K); (a) free **1**; (b) ca. 3 equiv. of $ZnCl_2$ was added to **1**.

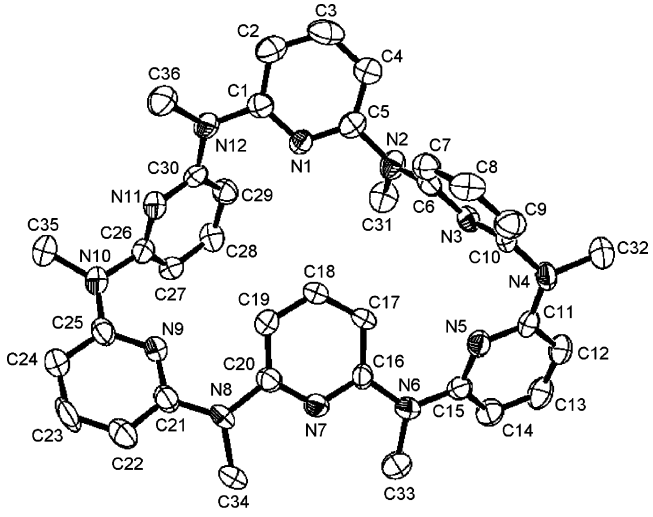

Figure 1. X-Ray crystal structure of **2** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

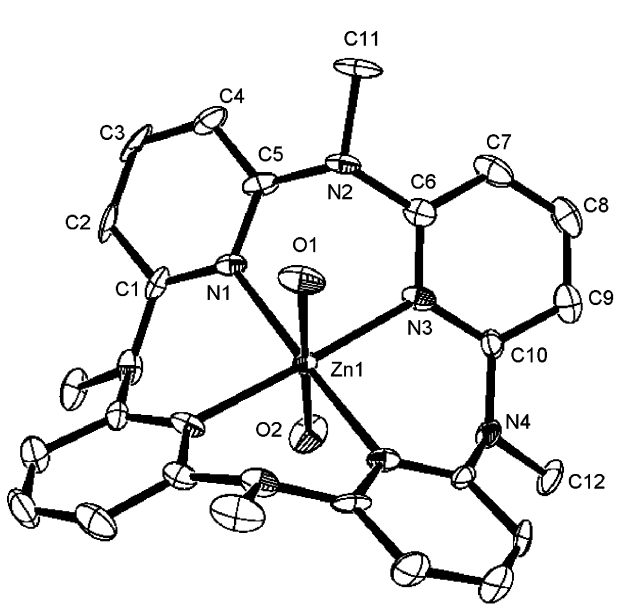

Figure 3. X-Ray crystal structure of zinc complex of **1** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms and $ZnCl_4^{2-}$ anion are omitted for clarity.

twisted from side to side to the medium plane defined by four pyridine nitrogen atoms. The bridging amine groups of **1** do not participate in the coordination toward zinc ion, and alternately deviate to either side of the medium plane in the solid state. The Zn–N bond lengths are in a 2.10(1)–2.13(1) Å range, comparable to or somewhat longer than the corresponding lengths found for $[Zn(bis(2,2'\text{-dipyridylamine}))_2]^{2+}$.[12] The Zn–O bond lengths (2.18(1)–2.29(1) Å) are also in the range expected for the zinc aqua complexes.[14] The general structural features of Zn complexes with 2,2′-dipyridylamine derivatives are in somewhat distorted tetrahedron geometry,[12,15] whereas the molecular structure of **1** in the Zn complex of **1** is reminiscent of the porphyrin analogs. These results suggest that the cyclization concentrates *N*-donor atoms in the cavity and zinc ion is complementarily included in the macrocyclic ligand.

Reaction of **2** with $ZnCl_2$ in CD_3CN also led to the downfield shifts and an appearance of broad signals at δ 7.80, 7.04, and 3.51 in the ^1H NMR spectrum suggested that **2** also included the zinc(II) ion. However, isolation of Zn complex of **2** has not been achieved. Further investigation on the complexation of the macrocycles would be required.

As described above, new macrocycles, azacalix[*n*]-(2,6)pyridines ($n=4$ and 6) have been prepared by the Pd-catalyzed aryl amination. Since the nitrogen lone pair electrons offer donor site in the cavity, zinc(II) ion coordinates to the macrocycles. Compounds **1** and **2** would furnish promising perspectives to form inclusion complexes with various metals and organic molecules. Attempts to optimize the preparation conditions and to examine their inclusion behaviors are being undertaken.

Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre; publication numbers CCDC 183231 (**2**) and 191021 ($[Zn^{II}\mathbf{1}(H_2O)_2][ZnCl_4]$).

Acknowledgements

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8. A mixture of 2,6-dibromopyridine (1185 mg, 5 mmol) and 2,6-bis(methylamino)pyridine (686 mg, 5 mmol) was dissolved in toluene (250 cm^3). Sodium-*tert*-butoxide (1142 mg, 15 mmol), tris(dibenzylideneacetone)dipalladium(0) (230 mg, 0.25 mmol), and tri-*tert*-butylphosphine (152 mg, 0.75 mmol) were added to the solution. The reaction mixture was stirred at 70°C for 72 h under N_2. The reaction mixture was quenched by adding aqueous ammonia and extracted with toluene. The organic fraction was concentrated, and the crude product was purified by column chromatography on alumina and an aminopropylated silica gel. The Pd-catalyzed aryl amination of 2-bromo-6-(methylamino)pyridine was carried out analogously. Compound **1**: FAB-MS: m/z 424; ^1H NMR (400 MHz in $CDCl_3$): δ 7.35 (t, $J=8.3$ Hz, 4H), 6.35 (d, $J=8.3$ Hz, 8H), 3.20 (s, 12H); ^{13}C NMR (100 MHz in $CDCl_3$): δ 159.1, 138.3, 108.5, 36.6. Compound **2**: FAB-MS: m/z 636; ^1H NMR (400 MHz in $CDCl_3$): δ 7.37 (t, $J=8.3$ Hz, 6H), 6.35 (d, $J=8.3$ Hz, 12H), 3.46 (s, 18H); ^{13}C NMR (100 MHz in $CDCl_3$): δ 156.0, 138.2, 107.0, 36.1.
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was solved by direct method (SIR-92) and expanded by using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least squares refinement was based on 2215 observed reflections ($I>3\sigma(I)$, 433 variable parameters) with factors of $R=0.056$, $Rw=0.078$, GOF = 1.08.

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13. Crystallographic data for $[Zn^{II}\mathbf{1}(H_2O)_2][ZnCl_4]$: $C_{24}H_{24}Cl_4N_8O_2Zn_2$, $M=729.08$, monoclinic, space group $C2/c$, $a=18.191(3)$, $b=12.389(3)$, $c=15.393(3)$ Å, $\beta=125.61(1)°$, $V=2820.4(1)$ Å^3, $Z=4$, $D_{calcd}=1.717$ g cm^{-3}, μ(Mo Kα) = 21.20 cm^{-1}, $T=296$ K, $F(000)=1472$. A total of 2988 reflections were measured, 2886 unique. The structure was solved by direct methods (SAPI-90) and expanded by using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least squares refinement was based on 2191 observed reflections ($I>3\sigma(I)$, 183 variable parameters) with factors of $R=0.110$, $Rw=0.223$, GOF = 1.54.
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