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Synthesis and Association Behavior of Butadiyne-Bridged [4$_4$](2,6)Pyridinophane and [4$_6$](2,6)Pyridinophane Derivatives

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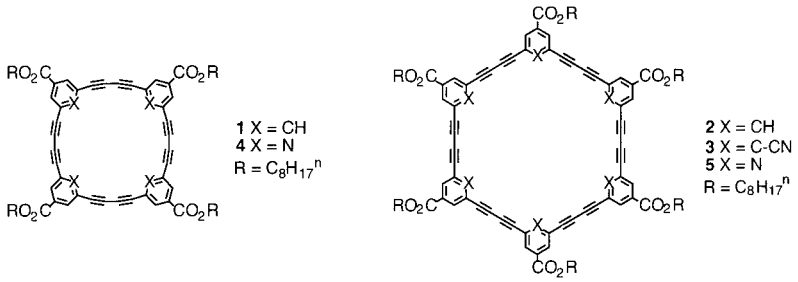
ABSTRACT



Butadiyne-bridged [4$_4$](2,6)pyridinophane and [4$_6$](2,6)pyridinophane derivatives were synthesized, and their heteroassociations with the corresponding metacyclophanes and complexations with organic cations were investigated.

Shape-persistent macrocyclic metacyclophanes with aromatic rings connected by triple bonds have been the subject of intensive study in view of their ability to self-associate and to bind large organic substrates.[1−4] We reported the synthesis of butadiyne-bridged [4$_4$]metacyclophane **1**[4a] and [4$_6$]metacyclophane **2**[4b] and their self-association behavior in solution. Moreover, we found that [4$_6$]metacyclophane **3** having *endo*-annular cyano groups associated in solution with **2** to form heteroaggregates and that **3** bound organic cations to form 2:1 (host:guest) complexes.[4b] As an extension of this work, we report here the synthesis and the association and complexation behaviors of butadiyne-bridged [4$_4$](2,6)-pyridinophane derivative **4** and its [4$_6$] congener **5**. Since the [4$_4$]metacyclophane with cyano groups as the nitrogen binding units, which corresponds to **4**, was not obtained because of the repulsive interaction between the cyano groups,[4b] compound **3** represents the smallest member of the series of [4$_n$]metacyclophanes having *endo*-annular binding functionalities. Pyridinophane **5** should possess a larger cavity than that of cyanocyclophane **3** while keeping the planarity of the macrocyclic ring.[5] It turned out that pyridinophanes **4** and **5** exhibit association and binding behaviors similar to those of cyanomacrocycle **3**.

The syntheses of **4** and **5** are outlined in Scheme 1. *n*-Octyl ester **6**, which was prepared by condensation of dichlorocitrazinic acid[6] with 1-octanol, was converted to the bis-

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(5) The diagonal N−N distances of **3** and **5** estimated from their AM1-optimized structures are 11 and 15 Å, respectively. The corresponding distance of **4** is 10 Å.

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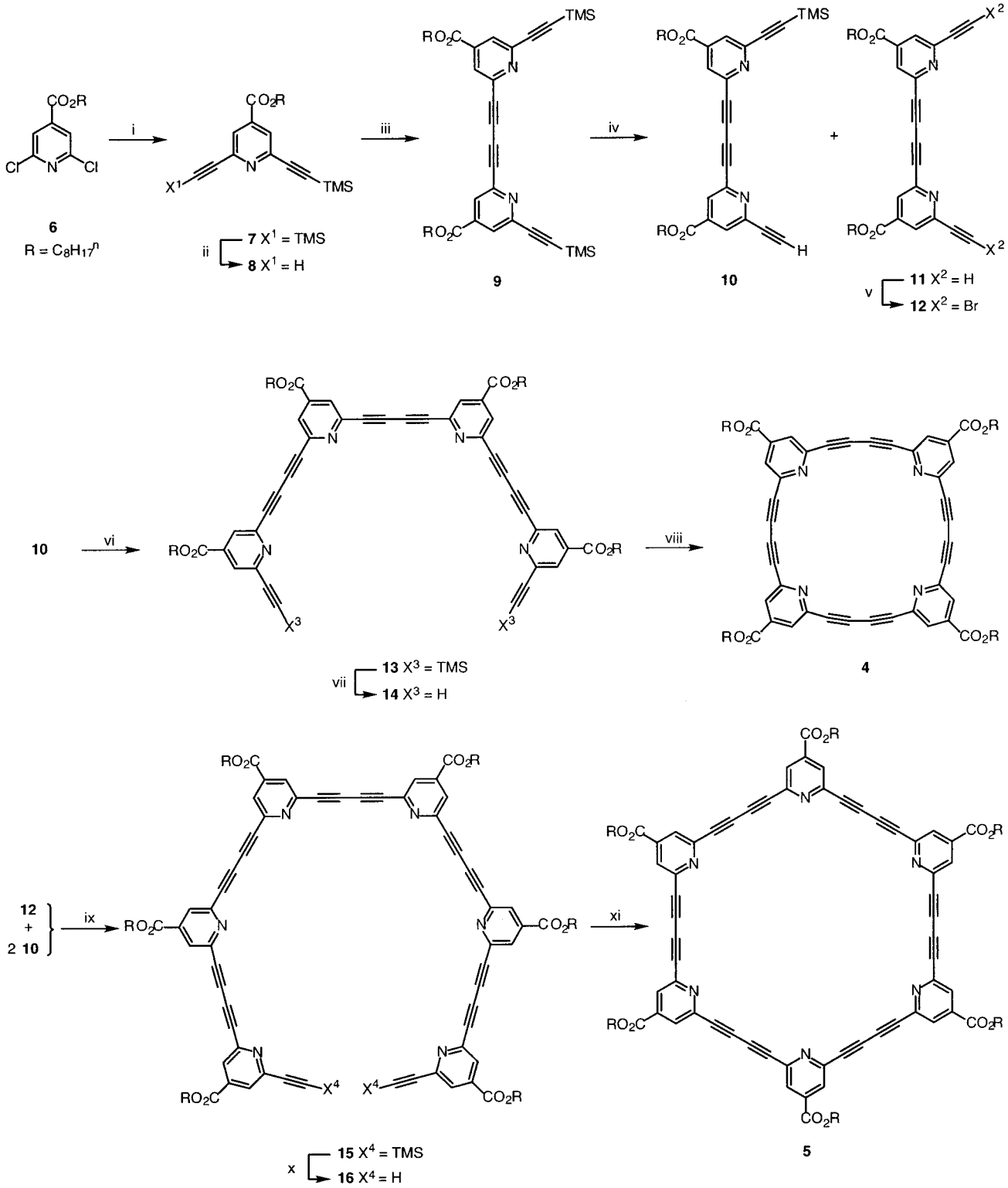
Scheme 1[a]



[a] (i) Trimethylsilylacetylene, $Pd_2(dba)_3$·$CHCl_3$, CuI, Ph_3P, Et_3N, 70 °C, 94%; (ii) K_2CO_3, H_2O, THF, rt, 36%, fully deprotected compound isolated in 37%; (iii) CuCl, TMEDA, O_2, acetone, rt, 90%; (iv) K_2CO_3, H_2O, THF, rt ,**10** 45% **11** 38%; (v) NBS, $AgNO_3$, acetone, rt, 80%; (vi) CuCl, TMEDA, O_2, acetone, rt, 89%; (vii) K_2CO_3, H_2O, THF, rt, 80%; (viii) $Cu(OAc)_2$, pyridine, benzene, rt, 50%; (ix) $Pd_2(dba)_3$·$CHCl_3$, CuI, $(furyl)_3P$, pentamethylpiperidine, benzene, rt, 38%; (x) Bu_4NF, AcOH, H_2O, THF, rt, 80%; (xi) $Cu(OAc)_2$, pyridine, benzene, rt, 29%. R is *n*-octyl group.

(trimethylsilyl)ethynyl derivative **7** by Sonogashira coupling.[7] Removal of the TMS group gave singly deprotected compound **8** (36%) together with doubly deprotected compound (37%) and unreacted **7** (19%) which were cleanly separated

by silica gel chromatography. Oxidative coupling[8] of **8** afforded dimer **9** which was treated with potassium carbonate to give partially deprotected **10** (45%), thoroughly deprotected **11** (38%), and recovered **9** (12%). Oxidative coupling[8] of **10** afforded linear tetramer **13**, and removal of the TMS group gave **14**. Intramolecular oxidative coupling of **14** under high dilution conditions by Eglinton's method[9] yielded cyclic tetramer **4** in 50% yield. Palladium-catalyzed heterocoupling[10] of dibromide **12**, prepared by bromination of **11** with NBS, with 2 equiv of **10** gave linear hexamer **15**. Deprotection of **13** gave unstable hexamer **16** which was subjected to intramolecular coupling to furnish cyclic hexamer **5** in 29% yield.

Pyridinophanes **4** and **5** did not show concentration dependence in the ^{1}H NMR spectra in $CDCl_3$ (10^{-2}−10^{-4} M), indicating that these did not tend to self-associate. This is probably due to the electrostatic repulsion between the nitrogen atoms,[4b] as indicated by the electrostatic potential plot (Figure 1) based on the AM1 method for the respective

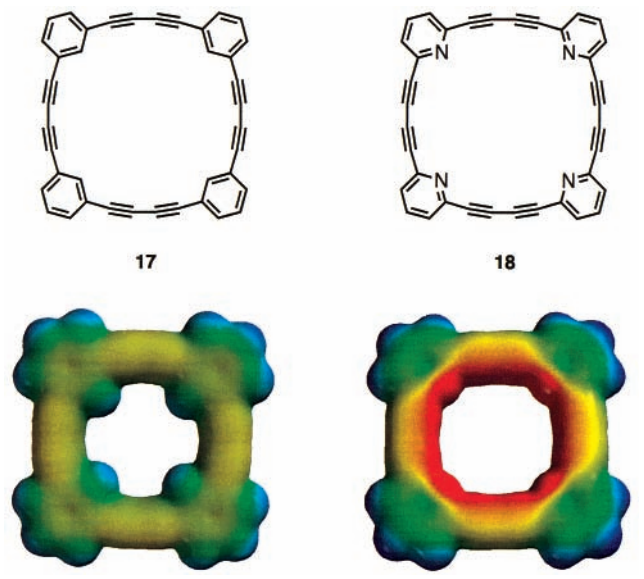


Figure 1. Electrostatic potentials between −19 (red) to 20 (blue) kcal/mol on the van der Waals molecular surface of the model compounds **17** and **18** according to the AM1 calculations.

model compounds **17** and **18** for the tetramers **1** and **4**.[11] On the other hand, the aromatic protons of **4** and **5** moved upfield on addition of the corresponding metacyclophanes **1** and **2** having the same macrocyclic ring size as shown in Figure 2. The chemical shift change of **4** shown in Figure 2 was

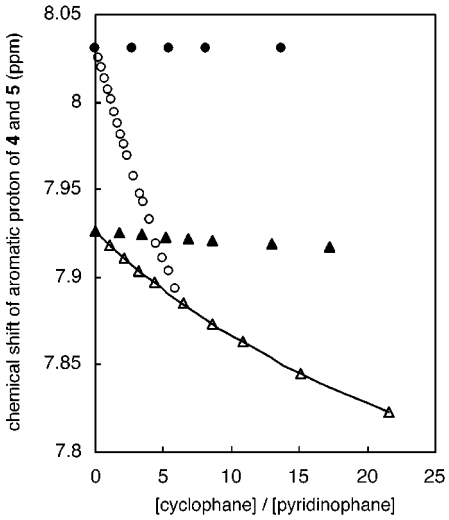


Figure 2. ^{1}H NMR titration of **4** and **5** with metacyclophanes **1** and **2** in $CDCl_3$ at 30 °C following the chemical shift change of the aromatic protons of **4** and **5**: ▲, **4** and **2**; △, **4** and **1** with a theoretical curve obtained by nonlinear least-squares analysis; ●, **5** and **1**; ○, **5** and **2**.

analyzed by assuming the formation of homodimer of **1** with a known dimerization constant of K_1 (26 M^{-1} at 30 °C)[4] and of heterodimer **1·4** with an association constant of K_2. The nonlinear least-squares approximation yielded K_2 of 72 M^{-1}. In the case of heteroassociation between hexamers **2** and **5**, however, similar treatment of the experimental data did not give a good fit. This means that the tetramers **1** and **4** form a dimer **1·4** mainly whereas the hexamers **2** and **5** aggregate to form dimer **2·5** and higher aggregates.[12] A similar tendency to form higher aggregates was observed in the hetetoaggregation between hexamer **2** and its cyano derivative **3**.[4b] By contrast, the chemical shifts of the aromatic protons of **4** and **5** did not change upon addition of **2** and **1**, respectively, having different macrocyclic ring size as shown in Figure 2. We assume that the driving force for the heteroaggregate formation is dipole−dipole interaction between the pyridine rings of **4** and **5** and the benzene rings of **1** and **2**.[13] Since the dipoles of the individual aromatic ring are arranged along the periphery of the planar macrocycle, the macrocycles have no or, if any, little dipole moment. Accordingly, the overall interaction between pyridinophanes **4** and **5** and cyclophanes **1** and **2** is similar to the quadrupole−quadrupole interaction between the aromatic rings substituted by electron-donating and -accepting groups.[14] Such interaction should be sensitive to the shape of the interacting molecules because the mutual overlap of the rings

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(11) The AM1 calculations were performed using the SPARTAN ver. 5.0 program package; Wavefunction, Inc., Irvine, CA.
(12) An attemped nonlinear least-squares analysis of the data assuming the formation of a heterodimer (with K_2) and a heterotrimer (with K_3) did not give a unique solution.
(13) The calculated (AM1) dipole moment of methyl 2,6-diethynylpyridine-4-carboxylate (1.26 D) is pointing from C(4) to the nitrogen atom, whereas that of methyl 3,5-diethynylbenzoate (0.85 D) is pointing to the opposite direction, i.e., to the ester group.

is essential to the interaction. The stronger tendency of **2** and **5** to form heteroaggregates than that of **1** and **4** is ascribed to the larger number of the sites of the attractive interaction.

To examine the binding ability of pyridinophanes **4** and **5** toward large organic cations, we selected the tropylium ion as a guest, even though it seems likely that the cation is slightly larger than the cavity of **4** but is too small to fit the cavity of **5**. The chemical shift change of the aromatic protons of **4** and **5** on titration with tropylium tetrafluoroborate in $CDCl_3/CD_3CN$ (17:3) at 30 °C was analyzed by assuming the formation of a 1:1 complex (with K_{11}) and a 2:1 complex (with K_{21}). The nonlinear least-squares regression analysis gave K_{11} and K_{21} to be 3×10^3 and 3×10^4 M^{-1} for **4** and 1×10^2 and 4×10^2 M^{-1} for **5**, respectively. The larger binding constants of **4** than those of **5** are ascribed to the size of the cavity of the former which fits better than that of the latter. It should be pointed out that all of the macrocycles **4**, **5**, and **3** form not only 1:1 but also 2:1 complexes, though the structures of those complexes are not known.

In summary, we synthesized butadiyne-bridged pyridinophanes **4** and **5** which form heteroaggregates in solution with the corresponding metacyclophanes **1** and **2** having the same macrocyclic ring size and are capable of binding tropylium cation to form 1:1 and 2:1 complexes. Further work on the construction of supramolecular assemblies using these molecular units is in progress.

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Supporting Information Available: Experimental procedure and characterization of compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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