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Synthesis of $[3_5]$(1,2,3,4,5)Cyclophane1)

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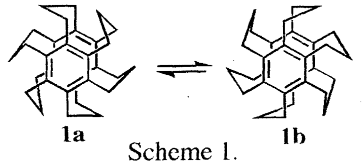
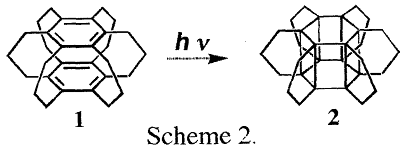
$[3_5]$(1,2,3,4,5)Cyclophane 3 was synthesized by an acid-catalyzed cyclization between a pseudogeminally substituted acetyl group and a chloromethyl group of a tetra-bridged compound followed by two-step hydrogenation of the resulting penta-bridged bromo-olefin. 3 shows the strongest transannular π–π interaction among [m.n]- and multibridged benzenophanes synthesized so far. 3 is conformationally mobile at room temperature in CD_2Cl_2, and two conformers 3a and 3b are observed at -90 °C.

$[3_6]$(1,2,3,4,5,6)Cyclophane 1 is one of the final target molecules in the field of [3.3]cyclophane chemistry. Structural and chemical features of 1 reside in its correlated flipping of six trimethylene bridges (Scheme 1)2) and predicted photochemical isomerization of 1 to propella$[3_6]$prismane 2 (Scheme 2).3) Our efforts toward the synthesis of 1 are being made via two approaches (Scheme 3): (a) a stepwise introduction of additional trimethylene bridges starting from $[3_3]$(1,3,5)cyclophane 5,4) and (b) a direct approach via cyclotrimerization of cyclodeca-1,6-diene 65) in the presence of a metal catalyst.6) Here we describe the synthesis via the route a, transannular π–π interaction, and stable conformations of $[3_5]$(1,2,3,4,5)cyclophane 3, which is a lower homologue of 1.



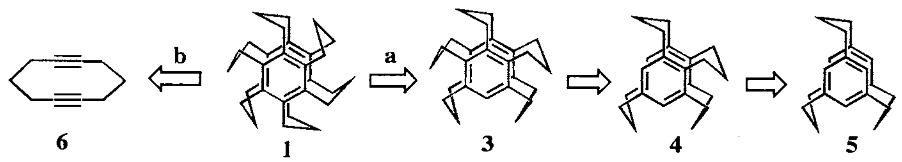
1a **1b**

Scheme 1.



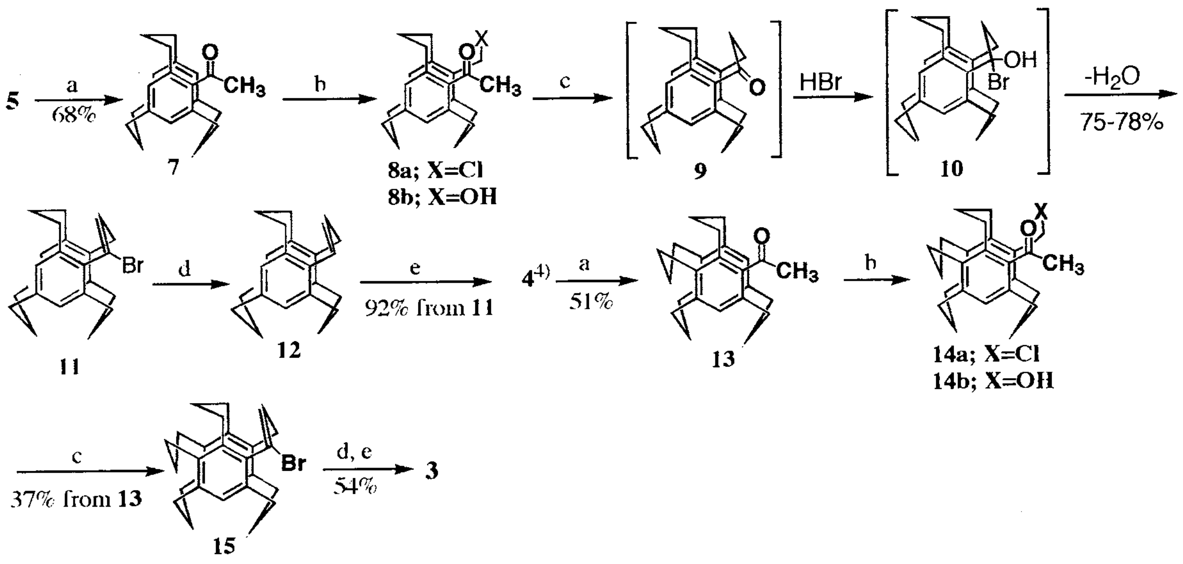
1 **2**

Scheme 2.



Scheme 3. Synthetic approaches: (a) stepwise approach (b) direct approach.

The most critical problem to be solved in the stepwise approach is to develop an efficient method for introducing a trimethylene bridge.[7] In the previous paper, we reported a solution to the problem; an acid-catalyzed reaction between the pseudogeminally substituted acetyl group and a chloromethyl group of tri-bridged cyclophane 8, followed by reduction of the resulting carbonyl group of 9 afforded tetra-bridged cyclophane 4 (40% from 7).[4] After we had reported the result, we found that simply the raise of the reaction temperature of the cyclization reaction to 130-140 °C resulted in the formation of bromo-olefin 11 in much higher yield (75-85%), presumably formed by the conversion of the ketone 9 to bromohydrin 10 and subsequent dehydration. The Pd/C (10%)-catalyzed hydrogenolysis of the bromine of 11 in the presence of KOH[8] followed by hydrogenation of the resulting olefin 12 afforded the tetra-bridged 4 (92% in two steps). The application of a similar series of reactions to chloromethyl compound 14a afforded penta-bridged cyclophane 3. Acetylation of 4 followed by chloromethylation provided the pseudogeminally substituted compound 14a. A similar acid-catalyzed cyclization reaction of 14 provided penta-bridged bromo-olefin 15 (37%), which was then converted into penta-bridged cyclophane 3 by the two-step hydrogenation as described above (54%).[9]



Scheme 4. Synthetic route to $[3_5](1,2,3,4,5)$cyclophane 3.
a) Ac_2O, $AlCl_3$, CS_2, reflux. b) $ClCH_2OCH_3$, $AlCl_3$, room temp. c) 30% HBr in AcOH/AcOH (2:1 v/v), 130-140 °C. d) 10% Pd/C, H_2 (1 atm), KOH, EtOH-THF, room temp. e) PtO_2, H_2 (1 atm), AcOH, room temp.

There is a marked tendency of gradually increasing transannular π-π interaction with the increase of the number of the trimethylene bridges; electronic absorption bands of 3 in CH_2Cl_2 [274 (ε 1250), 279 (ε 1370), 331nm (ε 59)] showed further bathochromic shifts as compared with the corresponding bands of 4 [269 (ε 1460), 275 (ε 1470), 321nm (ε 62)].4) In the charge transfer (CT) complexes between the cyclophane and tetracyanoethylene (TCNE), the CT band of 3 in CH_2Cl_2 (674 nm) significantly shifts to longer wavelength region compared with that of 4 (628 nm) in CH_2Cl_2. The value (674 nm) is the longest wavelength among those of the TCNE complexes of [m.n]cyclophanes and multibridged benzenophanes reported so far.

A sharp singlet of the aromatic protons at 6.71 ppm and well-time-averaged spectrum of the bridge protons (25 °C, $CDCl_3$), as well as four aromatic carbon and six bridge carbon signals of proton-decoupled ^{13}C NMR spectrum of 3 suggest a rapid flipping of the five trimethylene bridges. Both of the aromatic and trimethylene bridge protons exhibit strong temperature-dependent phenomena. The singlet of the aromatic protons at 23 °C (δ 6.71 ppm, CD_2Cl_2) broadens as the temperature is lowered, and finally resolved into two singlets at 6.58 and 6.82 ppm with the relative intensities being 1.0:1.2 at -90 °C. The energy barrier for this process is estimated to be 9.6 kcal/mol with T_c=-70 °C.10) Figure 1 denotes structures of MM3 optimized stable conformers of 3. **3b** is the most stable, and **3a** and **3c** are less stable by 0.69 and 1.31 kcal/mol, respectively (relative free energies at -90 °C). The predicted population of three isomers **3a**:**3b**:**3c** is 13:85:2 at -90 °C. Previously we reported that the chemical shifts of inner aromatic protons of [3.3]metacyclophanes are shielded in the following order: chair-chair>chair-boat>boat-boat.2a) Based on the predicted stability order as well as the lower chemical shift of the aromatic protons (6.82 ppm), the most stable isomer can be assigned to **3b**, whereas the other isomer with higher chemical shift (6.58 ppm) can be assigned to **3a** since the neighboring trimethylene bridges of the aromatic protons of **3a** and **3b** take chair-boat and boat-boat conformations, respectively. The MM3 estimated relative free energies of possible transition state structures (Fig. 2) for the flipping of the trimethylene bridges indicate that the energy barrier for flipping of the trimethylene bridge at C-2 and C-4 (**3e**, 5.4-6.7 kcal/mol) as well as C-3 (**3f**, 6.5 kcal/mol) is considerably reduced compared to those at C-1 and C-5 (**3d**, 9.5-10.4 kcal/mol).11) Although the detailed flipping processes of 3 have not been elucidated yet, the result suggests that the observed energy barrier (9.6 kcal/mol) is ascribed to that for the flipping of the bridge at C-1 and C-5.

Further study on the flipping process of 3 and the introduction of the final trimethylene bridge to 3 is now in progress.

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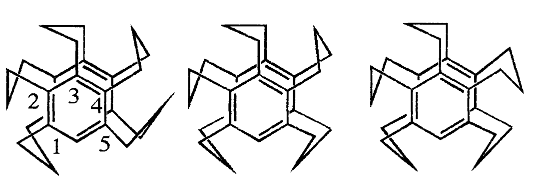
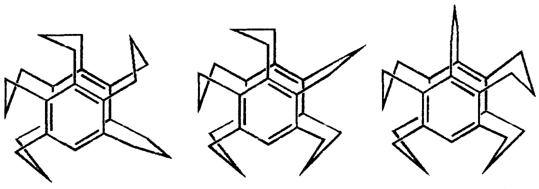


3a **3b** **3c**

Fig. 1. Stable conformers of **3**.



3d **3e** **3f**

Fig. 2. Possible transition state structures of **3**.

References

1) Part 2 of the series, "Multibridged [3_n]cyclophanes," Part 1 is Ref.4.

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9) Selected data for key compounds; 3: colorless crystals (hexane-CH_2Cl_2); mp 265-266.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.11-2.22 (m, 2H, -$CH_2CH_2CH_2$-), 2.33-2.56 (m, 8H, -$CH_2CH_2CH_2$-), 2.66-2.72 (m, 4H, -$CH_2CH_2CH_2$-), 3.05-3.26 (m, 16H, -$CH_2CH_2CH_2$-), 6.74 (s, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 21.8, 22.4, 27.7, 28.2, 29.4, 32.0, 132.0, 134.3, 137.4, 137.1. MS m/z (rel. int.): 356 (M^+, 100%). Anal. Found: C, 90.99; H, 9.01%. Calcd for $C_{27}H_{32}$: C, 90.95; H, 9.05%. 15: colorless crystals (hexane-CH_2Cl_2); mp 245-247.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.04-2.42 (m, 6H, -$CH_2CH_2CH_2$-), 2.59-3.32 (m, 18H, -$CH_2CH_2CH_2$-), 3.63 (d, J=4.4 Hz, 2H, -CH_2-CH=CBr-), 6.64 (t, J=4.4 Hz, 1H, -CH_2-CH=CBr-), 6.83 (s, 2H, aromatic). MS m/z (rel. int.): 432 (M^+, 98%), 434 (M^++2, 100%), 353 (M^+-^{79}Br, 48%). Anal. Found: C, 74.91; H, 6.77%. Calcd for $C_{27}H_{29}Br$: C, 74.82; H, 6.74%.

10) $\Delta G^{\neq}=RT_c(22.96+\ln T_c/\Delta\nu)$: $\Delta\nu=96.7$ Hz, $T_c=203$ K; I. C. Cadler and P. J. Garrat, *J. Chem. Soc. (B)*, 1967, 660.

11) The semiempirical MO calculations (PM3) also give a similar result. The computations were done with MM3-92 and MOPAC93 programs, graphically facilitated by ANCHOR II™ from Fujitsu Limited.

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