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Synthesis and guest-binding study of polytopic multi(cyclophane) hosts

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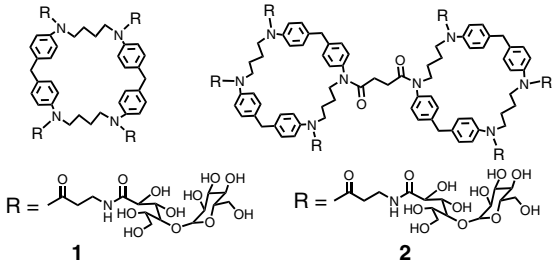
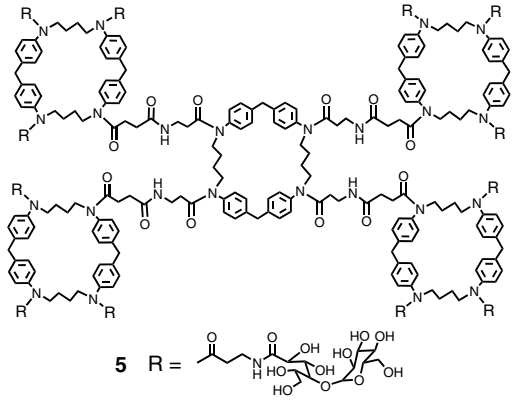
Abstract—Novel bis(cyclophanes) bearing glucosides and pentakis(cyclophanes) bearing glucosides were prepared as water-soluble hosts by connecting two or five macrocyclic skeletons, respectively. The guest-binding affinities of the present bis(cyclophanes) and pentakis(cyclophanes) toward a hydrophobic dye, 6-*p*-toluidinonaphthalene-2-sulfonate, were enhanced 13- and 1200-fold, respectively, relative to that by a corresponding monocyclic cyclophane, reflecting multivalency effects in macrocycles.

Cyclophanes play a broad and prominent role in supramolecular chemistry.[1] A number of cyclophane derivatives have been developed as hosts, and their guest-binding behaviors have been investigated.[2] Although moderate guest-binding ability has been exercised by various cyclophanes composed of a single macrocyclic skeleton, more sophisticated functions such as chiral recognition[3] and catalytic performance[4] can be achieved by appropriate modification of the cyclophane hosts. On the other hand, naturally occurring multivalent clusters of receptors are known to exhibit extremely strong binding capability toward substrates, even though individually these substrates bind only weakly to each other.[5] On these grounds, we designed novel polytopic multi(cyclophanes) hosts in order to enhance the guest-binding ability. Using a molecular design that allows the connection of two or five macrocyclic skeletons, bis(cyclophanes) **2** and pentakis(cyclophanes) **5** were prepared. In addition, maltosyl-derived substitutes were introduced into the multi(cyclophanes) to confer water solubility on the resulting hosts. We describe herein, the synthesis of bis- or pentakis(cyclophanes) (**2** and **5)** and their binding affinity based on multivalent systems toward hydrophobic guests as compared with those of the corresponding monocyclic cyclophane **1**[6] in aqueous media.





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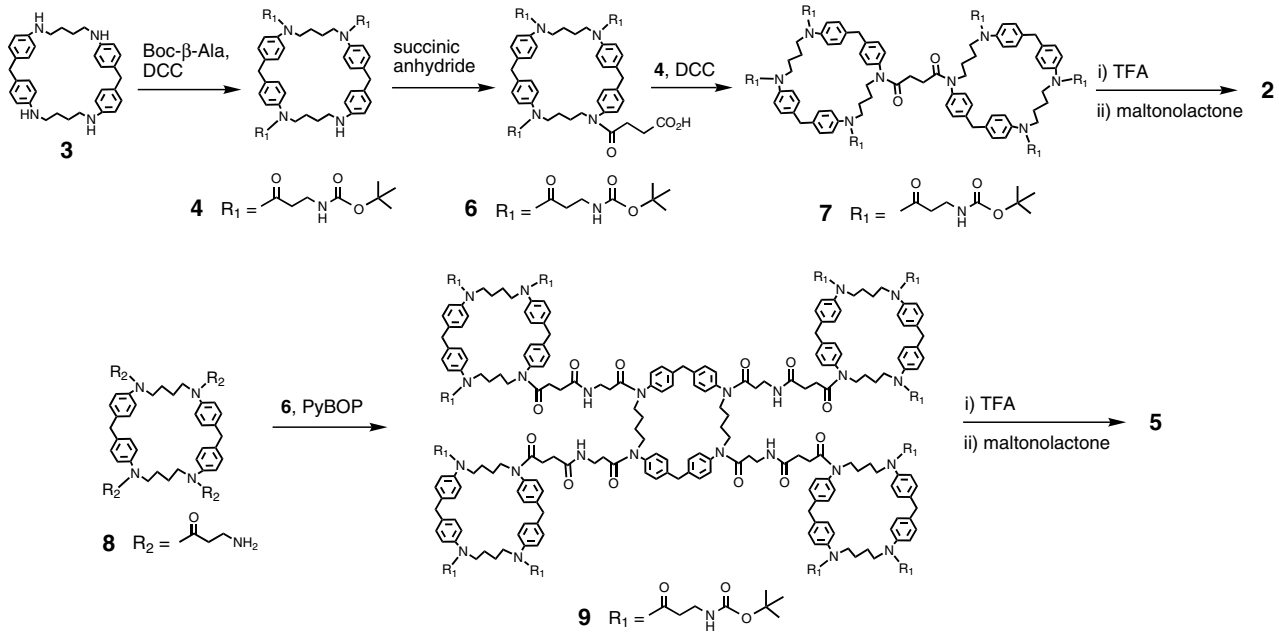

Scheme 1. Preparation of saccharide multi(cyclophanes).

We have focused on tetraaza[6.1.6.1]paracyclophane (**3**),[7] prepared by Koga and co-workers, as a macrocyclic framework for the construction of multi(cyclophanes) because durene, a guest molecule, was accommodated in its hydrophobic cavity, as confirmed by X-ray structural analysis. Bis(cyclophanes) having glucosides **2** and pentakis(cyclophanes) having glucosides **5** were prepared by following the reaction sequence given in Scheme 1. Tris(Boc-β-alanyl)-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (**4**)[9] was synthesized by condensation of **3** with Boc-β-alanine (3.0 equiv) in the presence of dicyclohexylcarbodiimide (DCC) in a 33% yield.[8] A cyclophane having a carboxylic acid (**6**)[9] was derived from **4** by a reaction with succinic anhydride and isolated as a carboxylic acid. A precursor (**7**)[9] of **2** was prepared by condensation of **4** with **6** in the presence of DCC. Bis(cyclophanes) derivative **2**[9] was obtained by the reaction of maltonolactone with a hexaamine derivative of bis(cyclophanes), which was prepared by removal of the protecting groups of **7**. A precursor (**9**)[9] of **5** was prepared by condensation of a tetraamine derivative of cyclophane **8**[10] with **6** in the presence of benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate (PyBOP). Pentakis(cyclophanes) **5**[9] was prepared from **9** in a manner similar to that applied to the synthesis of **2**. Both cyclophanes **2** and **5** had good H_2O-solubility of >1 g/mL. Furthermore, they were not self-aggregated, at least at 1 mM in water, as confirmed by dynamic light scattering (DLS) and surface tension measurements.

The effects of multivalent macrocycles on the guest-binding of **2** and **5** were examined by fluorescence spectroscopy at 293 K toward well-known fluorescent guests such as 6-*p*-toluidinonaphthalene-2-sulfonate (TNS) and 8-anilino-naphthalene-1-sulfonate (ANS), whose emission is extremely sensitive to change in the microenvironmental polarity experienced by the molecule. The fluorescence intensity originated from TNS (1.0 and 0.25 μM for **2** and **5**, respectively) increased upon addition of the cyclophanes as a host, as shown in Figure 1.

The stoichiometry for the complex was confirmed to be 1:1 host–guest by a Job plot (Fig. 2). Even though these hosts contain multiple hydrophobic cavities, they did not simultaneously incorporate more than two anionic guest molecules due to an electrostatic repulsion under these conditions. The 1:1 binding constants (K) of **2** and **5** toward TNS were evaluated on the basis of the Benesi–Hildebrand relationship and are summarized in Table 1 together with the corresponding value for **1**. Increases in the K values of **2** and **5** relative to **1** (13- and 1200-fold, respectively) can be regarded as a 'multivalency effect' that is exhibited by the bis- and pentakis(cyclophanes), respectively.[11,12] A similar binding trend was also confirmed for the complexation of these macrocycles with ANS (Table 1). In addition, the fluorescence maxima of the entrapped TNS by **1**, **2**, and **5** were almost the same (428, 430, and 429 nm, respectively). These results indicated that the microenvironmental polarity experienced by the incorporated guest molecules was nearly equal, even if the number of cyclophanes increased. The microenvironmental polarity experienced by the incorporated TNS molecule was evaluated from the fluorescence maximum in a manner similar to that reported previously.[13] The micro-environmental polarity parameter, E_T^N[14] for TNS placed in **2** and **5** was estimated to 0.68, which was equivalent to the E_T^N value for ethanol (0.654).

In conclusion, water-soluble bis(cyclophanes) and pentakis(cyclophanes) were synthesized on the basis of a molecular design that allows the connection of two or

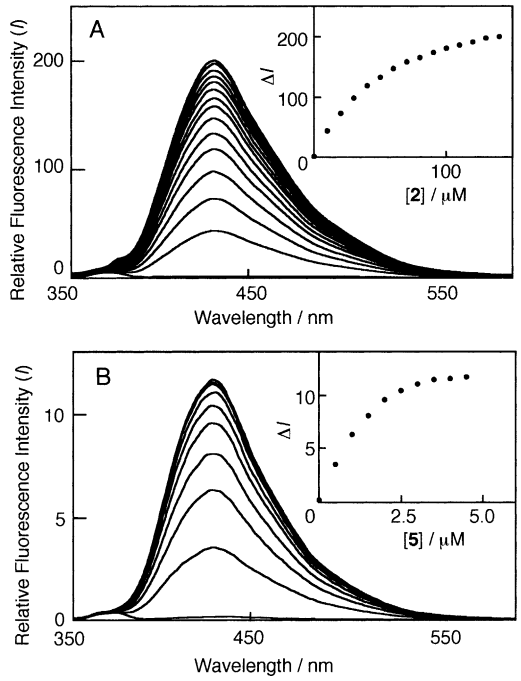

Figure 1. Fluorescence spectral changes for aqueous solution of TNS (1.0 and 0.25 μm for **2** and **5**, respectively) upon addition of **2** (A) of **5** (B) in water at 293 K: [**2**] = 0, 10, 20, 30, 40, 50, 60, 80, 90, 100, 110, 120, 130, and 140 μM, [**5**] = 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 4.5 μM (from bottom to top). Inset: the corresponding titration curve.

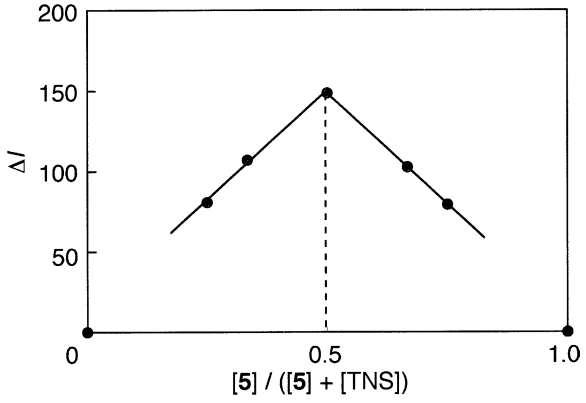

Figure 2. Job's plot for complex formation of **5** with TNS; total concentration of **5** and TNS, 3.0 μM.

Table 1. Binding constants (K, M^{-1}) for host–guest complexes of cyclophanes with TNS and ANS in water at 293 K

Host	K, M^{-1} (λ_{ex}, nm; λ_{em}, nm)[a]	
	TNS	ANS
1	1.6×10^3 (324; 428)	1.5×10^3 (375; 459)
2	2.0×10^4 (324; 430)	1.1×10^4 (375; 460)
5	1.9×10^6 (324; 429)	1.1×10^6 (375; 458)

[a] Excitation and emission maxima are given in parentheses, in this sequence.

five macrocyclic skeletons, respectively. The guest-binding affinity of the present multi(cyclophanes) toward hydrophobic dyes was much enhanced, reflecting multivalency effects in macrocycles. Moreover, the present multi(cyclophanes) display multivalent glucosides on the periphery on the cyclophanes, which can be recognized by carbohydrate-binding protein (lectin). The resulting multi(cyclophanes) having strong guest-binding affinity were expected to be used in saccharide-directed delivery of guests to the specific saccharide-binding surfaces.

Acknowledgements

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References and notes

1. Vögtle, F.; Seel, C.; Windscheif, P.-M. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2, Chapter 7, pp 211–265.
2. Odashima, K.; Koga, K. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2, Chapter 5, pp 143–194.
3. (a) Zhang, X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313–3361; (b) Rebek, J., Jr. *Chem. Commun.* **2000**, 637–643; (c) Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 2068–2078.
4. (a) Ducry, L.; Diederich, F. *Helv. Chim. Acta* **1999**, *82*, 981–1004; (b) Feiters, M. C.; Rowan, A. E.; Nolte, R. J. M. *Chem. Soc. Rev.* **2000**, *29*, 375–384.
5. (a) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321–327; (b) Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555–578.
6. (a) Hayashida, O.; Hamachi, I. *Chem. Lett.* **2003**, *32*, 632–633; (b) Hayashida, O.; Hamachi, I. *J. Org. Chem.* **2004**, *69*, 3509–3516.
7. (a) Odashima, K.; Itai, A.; Iitaka, A.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504–2505; (b) Odashima, K.; Itai, A.; Iitaka, A.; Koga, K. *J. Org. Chem.* **1985**, *50*, 4478–4485.
8. Under the reaction condition, bis(Boc-β-alanyl)cyclophane and tetrakis(Boc-β-alanyl)-cyclophane were also obtained in 25% and 13% yield, respectively.
9. Compound **2**; ^{1}H NMR (600 MHz, DMSO-d_6–D_2O, 318 K): δ 1.31 (m, 16H), 2.0 (m, 12H), 3.2–4.0, 4.87 (carbohydrate), 3.9 (m, 8H), 7.1 (m, 16H), 7.3 (m, 16H). ^{13}C NMR (150 MHz, D_2O, 298 K): δ 25.4, 34.8, 35.4, 46.5, 61.3, 63.3, 70.6, 72.6, 72.8, 73.0, 74.0, 83.7, 101.5, 126.3, 129.1, 130.7, 140.8, 141.5, 170.9, and 172.8. MS (MALDI-TOF) m/z 3584.82 $[M+Na]^+$. Found: C, 54.17; H, 6.79; N, 5.59. Calcd for $C_{162}H_{232}N_{14}O_{74}\cdot H_2O$: C, 54.39; H, 6.59; N, 5.48. Compound **4**: R_f (Wako Silica Gel 70FM, ethyl acetate) 0.60; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 1.45 (s, 31H), 1.57 (br, 4H), 2.1 (m, 6H), 3.08 (br, 2H), 3.3 (m, 6H), 3.61 (m, 4H), 3.67 (m, 2H), 3.83 (s, 2H), 3.98 (s, 2H), 5.32 (br, 3H), 6.4, 6.9, and 7.2 (m, 16H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 25.5, 25.8, 26.7, 28.8, 35.2, 36.7, 41.2, 44.0, 49.2, 79.4, 113.2, 128.6, 129.8, 130.7, 140.0, 140.8, 142.8, 146.9, 156.3, and 171.9. HRMS (FAB) calcd for $C_{58}H_{79}N_7O_9Na$: 1040.5837. Found: 1040.5853. Compound **5**: ^{1}H NMR (600 MHz, DMSO-d_6–D_2O, 298 K): δ 1.28 (m, 40H), 2.0 (br, 40H), 3.0–3.9, 4.86 (carbohydrate), 3.0–3.2 (m, 32H), 3.9 (br, 20H), 7.1 (m, 40H), 7.3 (m, 40H). ^{13}C NMR (150 MHz, D_2O, 298 K): δ 23.5, 31.2, 33.8, 35.6, 41.0, 47.7, 60.7, 62.5, 71.6, 72.0, 72.1,

72.7, 72.9, 73.0, 73.2, 73.3, 73.3, 73.6, 74.4, 74.9, 76.6, 77.0, 77.2, 82.4, 82.8, 92.2, 96.1, 101.0, 130.5, 139.4, 141.3, 172.8, 173.8, 174.2, and 178.6. MS (MALDI-TOF) m/z 8094.12 $[M+Na]^+$. Found: C, 54.77; H, 6.69; N, 6.08. Calcd for $C_{378}H_{528}N_{36}O_{156}\cdot 12H_2O$: C, 54.60; H, 6.69; N, 6.26. Compound **6**: ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 1.43 (s, 35H), 2.1 (br, 6H), 2.23 (br, 2H), 2.57 (br, 2H), 3.27 (br, 6H), 3.64 (br, 8H), 4.0 (s, 4H), 5.36 (br, 3H), 7.0 (m, 8H), and 7.2 (m, 8H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 25.3, 28.8, 30.1, 35.2, 36.7, 41.4, 49.1, 49.4, 53.9, 79.4, 128.7, 130.6, 140.8, 140.9, 156.4, 171.9, and 175.5. HRMS (FAB) calcd for $C_{62}H_{84}N_7O_{12}$: 1118.6178. Found: 1118.6174. Compound **7**: R_f (Wako Silica Gel 70FM, chloroform–methanol, 10:1 v/v) 0.40; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 1.42 (s, 70H), 2.1 (m, 16H), 3.26 (br, 12H), 3.6 (m, 16H), 3.95 (s, 8H), 5.32 (br, 6H), 6.9, and 7.2 (m, 32H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 25.3, 28.9, 35.2, 36.7, 41.5, 49.0, 79.4, 128.8, 130.6, 140.6, 140.9, 156.3, and 171.8. HRMS (FAB) calcd for $C_{120}H_{160}N_{14}O_{20}Na$: 2140.1831. Found: 2140.1873. Compound **9**: R_f (Wako Silica Gel 70FM, chloroform–methanol, 10:1 v/v) 0.6; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 1.43 (s, 140H), 1.82 (br, 8H), 2.1 (m, 40H), 2.2 (m, 8H), 2.3 (m, 8H), 3.2 (br, 8H), 3.2 (br, 24H), 3.3 (br, 8H), 3.6 (br, 40H), 3.9 (s, 20H), 5.35 (br, 12H), 6.6, 6.9, 7.0, and 7.2 (m, 84H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 25.4, 26.8, 28.8, 30.2, 31.8, 35.2, 36.7, 40.6, 41.4, 42.2, 46.7, 49.1, 79.3, 128.8, 130.6, 140.6, 140.9, and 156.3, and 171.8. MS (MALDI-TOF) m/z 5210.82 $[M+Na]^+$.

10. (a) Hayashida, O.; Hamachi, I. *Chem. Lett.* **2003**, *32*, 288–289; (b) Hayashida, O.; Hamachi, I. *Chem. Lett.* **2004**, *33*, 548–549.
11. Thermodynamic parameters (ΔH/kJ mol^{-1} and $T\Delta S$/kJ mol^{-1}) were also evaluated from temperature-dependent K values for hosts **1**, **2**, and **5** with TNS; the resulting values were −13.3 and 4.0, −13.0 and 10.4, −11.4 and 22.8, respectively. The effect of multivalent macrocycles **2** and **5** seems to be reflected in the more positive entropy ($T\Delta S$) contributions to the binding.
12. (a) Multivalency effect by polytopic hosts in organic solvents; Fulton, D. A.; Cantrill, S. J.; Stoddart, J. F. *J. Org. Chem.* **2002**, *67*, 7968–7981; (b) James, N. L.; Fulton, D. A.; Chiu, S.-H.; Elizarov, A. M.; Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *J. Org. Chem.* **2004**, *69*, 4390–4402.
13. Hayashida, O.; Ono, K.; Murakami, Y. *Tetrahedron* **1995**, *51*, 8423–8436.
14. Reichardt, C. *Solvents and Solvent effects in Organic Chemistry*; VCH Verlagsgesellschaft: Weinheim, 1988, Chapter 7.