

A new self-assembling capsule *via* metal coordination†

Takeharu Haino,* Mutsumi Kobayashi, Midori Chikaraishi and Yoshimasa Fukazawa*

Received (in Cambridge, UK) 23rd February 2005, Accepted 18th March 2005

First published as an Advance Article on the web 7th April 2005

DOI: 10.1039/b502598b

A new octadentate cavitant forms a stable dimeric molecular capsule *via* metal-coordination, creating a large and elaborate three-dimensional cavity in which large aromatic guests are accommodated to form supramolecular complexes.

There is considerable interest in constructing nano size supra-molecular hosts *via* self-assembly of molecular precursors.¹ Such large and elaborate molecular architectures offer well-defined inner cavities capable of carrying fascinating functions: encapsulation of a large molecular guest or several guests,² stabilizing unstable intermediates,^{3,4} as molecular catalysts^{5,6} *etc.* These properties are unique to the assembled state, and depend on the size and nature of the cavities. Thus the development of a new class of nano size capsules *via* self-assembly offers the possibility to create novel functions. The resorcinarene-based cavitants are potential building blocks for creating self-assembling molecular capsules driven by hydrogen bonding^{1–3,5} and metal-coordination.⁷ We report here a new class of the metal-assisted self-assembling nano capsule **1·4BF₄** using octadentate cavitant **2** and its unique guest binding properties (Scheme 1).

The synthesis of **2** was achieved according to Scheme 2. Bipyridine unit **5** was prepared by Suzuki coupling of bromobipyridine **3**⁸ and **4**.⁹ Cavitant **6**¹⁰ was treated with *n*-BuLi, subsequent addition of iodine to give tetra-iodocavitant **7**. Suzuki coupling reaction¹¹ of **5** and **7** smoothly proceeded to give the desired octadentate cavitant **2**.

† Electronic supplementary information (ESI) available: experimental section, ESI MS of the capsule, and 2D spectra of the complexes. See <http://www.rsc.org/suppdata/cc/b5/b502598b/>

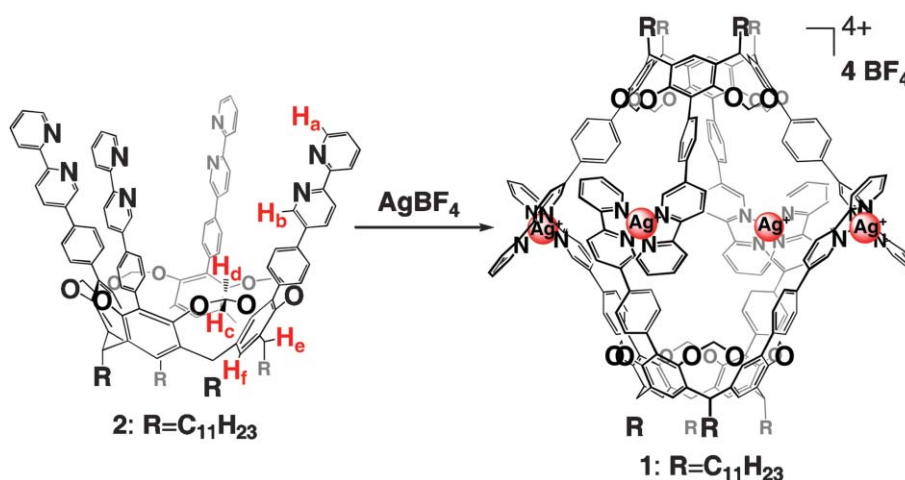
*haino@sci.hiroshima-u.ac.jp (Takeharu Haino)

Capsule **1·4BF₄** is formed instantly as a colorless solid by the simple addition of two equivalents of silver tetrafluoroborate to a solution of **2** in nitromethane. The structure of **1·4BF₄** was confirmed by elementary analysis, and ESI-MS.

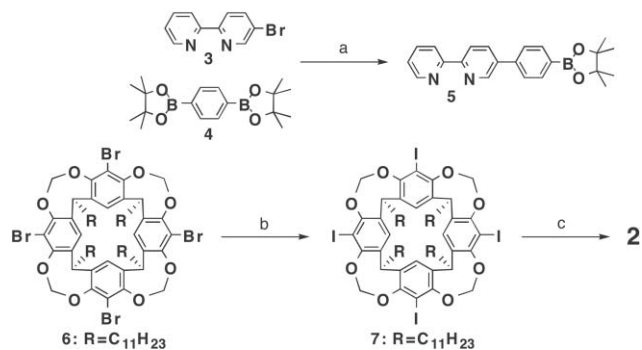
Many diastereomeric forms are possible for dimeric structure **1·4BF₄**; however, the ¹H NMR spectrum in CDCl₃ (Fig. 1) revealed the selective formation of the *D*₄ symmetric form in which the eight bipyridyl groups are magnetically equivalent. Pyridyl protons H_a and H_b showed upfield shifts as a consequence of the Ag–N bond formation. This rationalizes that a silver cation complexes to two bipyridines in a tetrahedral fashion; protons H_a and H_b stay in the shielding region of the other bipyridyl group and experience their shielding effect. While the precise reason for the selective formation of the *D*₄ form remains to be determined, the molecular modeling of **1·4BF₄** suggested that the *D*₄ symmetric form is more stable than the others.¹²

Diffusion coefficients *D* ($3.66 \pm 0.05 \times 10^{-10}$ and $4.79 \pm 0.04 \times 10^{-10}$ m² s⁻¹ for **1·4BF₄** and **2**) in chloroform were measured by pulsed field gradient NMR experiments using BPPSTE pulse sequence. The resulting ratio *D*_{dimer}/*D*_{mono} = 0.76 is in reasonable agreement with the theoretical ratio of 0.72–0.75 expected for a dimer¹³ and confirms the dimeric nature of the complex **1·4BF₄**.

The complex shows high kinetic stability in organic solution. When a chloroform-*d* solution of **1·4BF₄** was added to that of **2**, their sharp signals appeared independently; the traits support sizable energetic barriers between free and complexed states. 2D ROESY spectra of the mixture revealed that the dynamic exchange between them still exists, but the rate is slower than NMR time scale. In common Ag-bipyridine complexes the energetic barrier for the exchange between the free and the complexed states are



Scheme 1 Metal-induced capsule formation.



Scheme 2 Reagents and conditions. a) Pd(PPh₃)₄, Na₂CO₃, dioxane, H₂O 49%; b) n-BuLi, I₂, THF 79%; c) PdCl₂(PPh₃)₂, Ph₃As, Cs₂CO₃, 5, dioxane 80%.

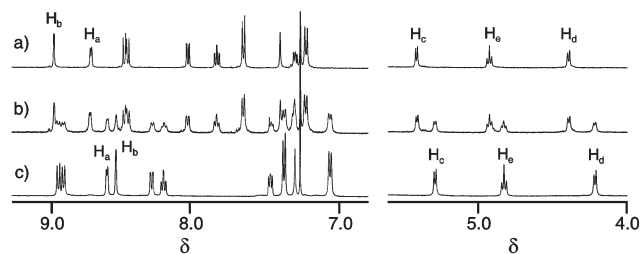


Fig. 1 ¹H NMR spectra (500 MHz) in chloroform-*d* at 298 K. a) **2** (1.0 mM); b) **1·4BF₄** (0.4 mM) and **2** (1.0 mM); c) **1·4BF₄** (1.0 mM).

small.¹⁴ This high kinetic stability of **1·4BF₄** would be a result of the cooperative complexation of the bipyridine units.

Rigid guests **8–13** allow us to measure the experimental interior dimension of the capsule (Fig. 2). 4,4'-Diacetoxybiphenyl **9** is readily encapsulated by **1** in CDCl₃, and the complex formed shows high kinetic and thermodynamic stability (Fig. 3a, Table 1). The large upfield shift of the guest methyl groups (δ : -1.37, $\Delta\delta$: -3.70 ppm) was observed. 2D NOESY spectrum showed strong intermolecular NOE cross-peaks between the methyl protons of the bound guest and the H_c, H_d and H_f protons on the resorcinarene platform. The large upfield shift and these NOE's are consistent with the binding conformation in which the two methyl groups are close to each end of the cavity. The complex of **10** also showed the high kinetic stability with the large upfield shift of the methyl group (δ : 0.4, $\Delta\delta$: -3.5 ppm) (Fig. 3b), but the association constant is about 200 times as small as that of **9** even though they have similar and complementary shapes (molecular lengths: 14.2 and 14.1 Å for **9** and **10**). It is known that the resorcinarene cavity creates CH/ π interaction to acidic protons,¹⁵ so that the more acidic methyl proton of **9** should drive the extremely high binding ability. In contrast, **8** did not complex whereas the other aromatic guests **11**, **12** and **13** were

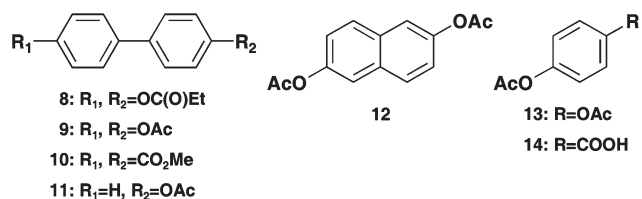


Fig. 2 Guests.

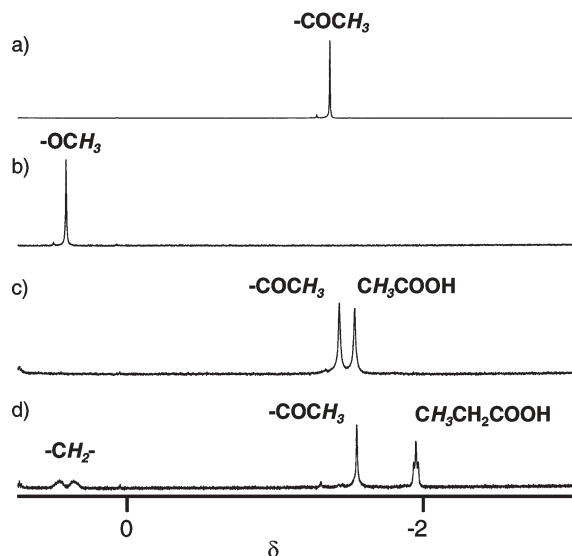


Fig. 3 The upfield region of the ¹H NMR spectra in chloroform-*d* of **1·4BF₄** (2.0~3.6 mM) with: a) **9** (1.5 eq.) at 298 K, b) **10** (1.0 eq.) at 298 K, c) the 1:1 mixture of **14** (3.5 eq.) and acetic acid (3.5 eq.) at 218 K, d) the 1:1 mixture of **14** (8.0 eq.) and propionic acid (8.0 eq.) at 218 K.

Table 1 Association constants^a K_a (M⁻¹) in CDCl₃

Guest	K _a	Guest	K _a
8	0	11	80 ± 10
9	82000 ± 6000	12	118 ± 5
10	410 ± 10	13	60 ± 8

^a Association constants were determined at 298 K.

encapsulated, but the time-averaged spectra were given. Accordingly, **9** and **10** establish the best complementary molecular length, about 14 Å.

Two different carboxylic acids form the statistical mixtures of the homo and the hetero hydrogen-bonded dimers in organic solution; however, the capsule enhanced the hetero dimerization of carboxylic acids.¹⁶ When a 1:1 mixture of acetic acid and **14** was added to the solution of **1·4BF₄**, an asymmetrically filled capsule was exclusively observed at 218 K (Fig. 3c). Two singlets appeared in the clear window higher than 0 ppm. Based on 2D ROESY experiment, they are assigned to the methyl groups of **14** and acetic acid (δ : -1.43; $\Delta\delta$: -3.8 ppm for AcO-, δ : -1.54; $\Delta\delta$: -3.7 ppm for acetic acid). These characteristic upfield shifts of the methyl groups and the integrations confirmed the formation of the hetero dimer of **14** and acetic acid in the capsule. Propionic acid also forms the hetero dimer with **14** in the capsule. The characteristic upfield shifts were observed for -CH₃ and -CH₂- of propionic acid ($\Delta\delta$: -3.1 and $\Delta\delta$: -2.0 ppm for -CH₃ and -CH₂-), placing both -CH₃ groups near the ends of the cavity (Fig. 3d).

The relative stability of the hetero dimers was assessed through the competition experiment. When acetic acid, propionic acid and **14** were added in a 1:1:1 ratio to a chloroform solution of **1·4BF₄**, the hetero dimer of **14** and acetic acid formed exclusively. The calculated structures suggest that both hetero dimers fit nicely inside and the methyl groups of acetic and propionic acids point down to the end of the cavity, creating CH/ π interactions (Fig. 4).¹² The more acidic methyl group of acetic acid receives more

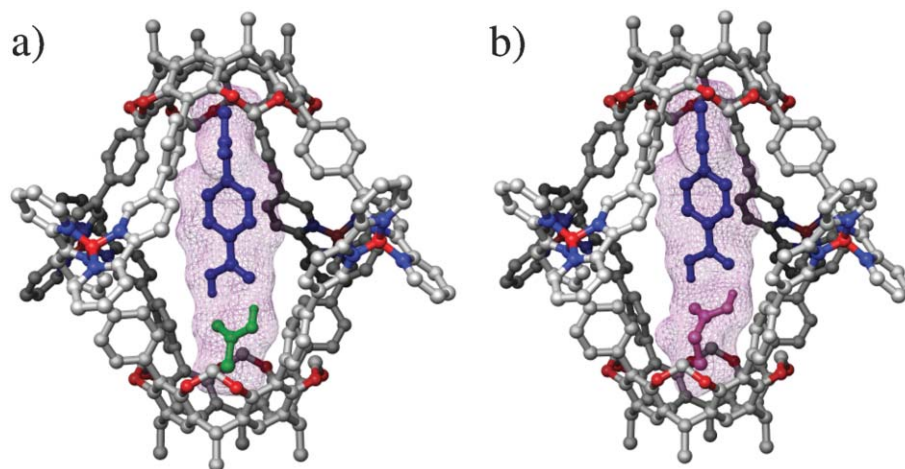


Fig. 4 Optimized structures of co-encapsulation complexes of **1** with **14** and: a) acetic acid; b) propionic acid.

attractive CH/ π interaction to the aromatic cavity than that of propionic acid. Accordingly, the acidity of the methyl groups most likely drives the selectivity.

In summary, we demonstrated the synthesis of self-assembled capsule **1-4BF₄** and its unique encapsulation properties, derived from its size and shape. Matching the overall length of the H-bonded pair of two different carboxylic acids with the dimension of the cavity results in the uncommon co-encapsulation with surprising selectivity. Further studies on the binding properties of **1-4BF₄**, as well as other related self-assembling capsules, are currently underway.

Takeharu Haino,* Mutsumi Kobayashi, Midori Chikaraiishi and Yoshimasa Fukazawa*

Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima, 739-8526, Japan.
E-mail: haino@sci.hiroshima-u.ac.jp; Fax: +81-82-424-0724;
Tel: +81-82-424-7403

Notes and references

- (a) F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2002, **41**, 1488–1508; (b) L. J. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.*, 2001, **40**, 2382–2426; (c) J. Rebek, Jr., *Acc. Chem. Res.*, 1999, **32**, 278–286.
- (a) T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 1998, **394**, 764–766; (b) M. Yamanaka and J. Rebek, Jr., *Chem. Commun.*, 2004, 1690–1691; (c) A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 12074–12075; (d) T. Amaya and J. Rebek, Jr., *Chem. Commun.*, 2004, 1802–1803.
- S. K. Körner, F. C. Tucci, D. M. Rudkevich, T. Heinz and J. Rebek, Jr., *Chem.–Eur. J.*, 2000, **6**, 187–195.
- T. Kusakawa and M. Fujita, *J. Am. Chem. Soc.*, 1999, **121**, 1397–1398.
- (a) B. W. Purse, P. Ballester and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 14682–14683; (b) J. Kang and J. Rebek, Jr., *Nature*, 1997, **385**, 50–52.
- (a) M. Yoshizawa, S. Miyagi, M. Kawano, K. Ishiguro and M. Fujita, *J. Am. Chem. Soc.*, 2004, **126**, 9172–9173; (b) M. Yoshizawa, Y. Takeyama, T. Kusakawa and M. Fujita, *Angew. Chem., Int. Ed.*, 2002, **41**, 1347–1349.
- (a) P. Jacopozi and E. Dalcaneale, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 613–615; (b) B. Bibal, B. Tinant, J.-P. Declercq and J.-P. Dutasta, *Chem. Commun.*, 2002, 432–433; (c) S. J. Park and J.-I. Hong, *Chem. Commun.*, 2001, 1554–1555; (d) K. Kobayashi, Y. Yamada, M. Yamanaka, Y. Sei and K. Yamaguchi, *J. Am. Chem. Soc.*, 2004, **126**, 13896–13897.
- F. M. Romero and R. Ziessel, *Tetrahedron Lett.*, 1995, **36**, 6471–6474.
- M. H. Todd, S. Balasubramanian and C. Abell, *Tetrahedron Lett.*, 1997, **38**, 6781–6784.
- P. Timmerman, H. Boerrigter, W. Verboom, G. J. Van Hummel, S. Harkema and D. N. Reinhoudt, *J. Inclusion. Phenom. Mol. Recognit. Chem.*, 1994, **19**, 167–191.
- L. Sebo, F. Diederich and V. Gramlich, *Helv. Chim. Acta*, 2000, **83**, 93–113.
- The molecular mechanics calculations were carried out by MacroModel V. 6.5 using amber* force field. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comp. Chem.*, 1990, **11**, 440.
- (a) M. S. Kaucher, Y.-F. Lam, S. Pieraccini, G. Gottarelli and J. T. Davis, *Chem.–Eur. J.*, 2005, **11**, 164–173; (b) F. W. Kotch, V. Sidorov, Y.-F. Lam, K. J. Kayser, H. Li, M. S. Kaucher and J. T. Davis, *J. Am. Chem. Soc.*, 2003, **125**, 15140–15150; (c) B. Olenyuk, M. D. Levin, J. A. Whiteford, J. E. Shield and P. J. Stang, *J. Am. Chem. Soc.*, 1999, **121**, 10434–10435; (d) A. S. Altieri, D. P. Hinton and R. A. Byrd, *J. Am. Chem. Soc.*, 1995, **117**, 7566–7567; (e) V. V. Krishnan, *J. Magn. Reson.*, 1997, **124**, 468–473.
- T. Haino, H. Araki, Y. Yamanaka and Y. Fukazawa, *Tetrahedron Lett.*, 2001, **42**, 3203–3206.
- (a) K. Kobayashi, Y. Asakawa, Y. Kikuchi, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, 1993, **115**, 2648–2654; (b) D. Falábu, A. Shivanyuk, M. Nissinen and K. Rissanen, *Org. Lett.*, 2002, **4**, 3019–3022.
- Benzoic acids and methylpyridone formed homo dimers in the self-assembled cylindrical capsule. T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 1999, **38**, 1136–1139.