Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry RSCPublishing

PAPER

Molecular recognition of upper rim functionalized cavitand and its unique dimeric capsule in the solid state

Mutsumi Kobayashi, Mei Takatsuka, Ryo Sekiya, and Takeharu Haino*

CaCite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

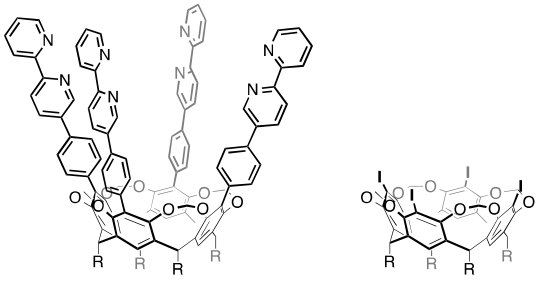
www.rsc.org/

Cavitand **1** possesses four 2,2'-bipyridyl pillars on its upper rim that encapsulates small guests, such as nitromethane, acetonitrile, methyl acetate, ethyl acetate, and *N*-methylacetamide, into a deep cavity to form host-guest complexes in a 1:1 ratio. Nitroethane, *N*,*N*-dimethylformamide, and *N*,*N*-dimethylacetamide were not bound in this manner. A guest-binding study and molecular mechanics calculations revealed that the four 2,2'-bipyridyl pillars of cavitand **1** created a steric boundary that is responsible for selective guest recognition. In the solid state, cavitand **2** formed a unique chiral capsule $\mathbf{2}_2$ by π-π stacking interactions between the 2,2'-bipyridyl pillars. A nitromethane molecule was unusually placed deep inside the cavity, as directed by the multiple hydrogen bonding interactions between the nitromethane oxygen atoms, the C–H bonds of the bridge methylenes and the pillar phenyl groups.

Introduction

Cavitands are synthetic hosts that consist of an enforced concave cavity surrounded by four aromatic rings, which are synthesized by covalent linkages between neighboring phenolic hydroxyl groups in a resorcinarene. They are frequently employed as molecular platforms for synthetic hosts due to their synthetic flexibility and ease of chemical modification.[1] Recent synthetic efforts have been directed toward extending the cavities into nanometric sizes to obtain applicable stability of host-guest complexes with high guest selectivity. Extending the cavities into nanometer sizes can be achieved in two ways: First, the direct chemical modification of the upper rim of a cavitand can bring in deeper cavitands;[2] and second, the self-assembly of two or more cavitands can result in cage-like capsules.[3] The nanometric cavities of the deep cavitands and capsules are large enough to bind sizable guests or even more than one guest molecule. The guest selectivity in regards to size and shape relies on structural complementarity between the guest and the cavity. Therefore, fundamental research into the molecular recognition of the cavitands and capsules is indispensable for directing the development of more sophisticated host-guest systems.

We have been studying the molecular recognition properties of cationic[4] and anionic[5] coordination capsules as well as their neutral components[6] in solutions and in the solid state. A cationic M_4L_2 coordination capsule was composed of four Ag^+ cations and two molecules of cavitand **1**, which each possesses four 2,2'-bipyridyl pillars on its upper rim (Fig. 1).[4a-c] The coordination capsule selectively encapsulated neutral organic molecules, such as 4,4'-diacetylbiphenyl derivatives[4b] and hydrogen-bonded carboxylic acid heterodimers[4a], to form stable host-guest complexes in ratios ranging from 1:1 to 1:2 depending on the molecular structures of the guests. The molecular recognition of cavitand **1** has not been studied yet. Studies on the guest recognition by cavitand **1** should provide valuable information for the development of new cavitand-based hosts as well as the recognition events in the dimeric capsule. Thus, we set out to study the guest recognition properties of the simple pillar introduced by cavitand **1**. In this paper, the molecular recognition of small organic guests **5**–**12** in chloroform-d_1 by cavitand **1** was achieved using the ^{1}H NMR titration technique (Fig. 2). The molecular modeling studies for the guest selectivity are also reported. The crystal structure of cavitand **2** with nitromethane **5** was successfully found using X-ray diffraction analysis, demonstrating that the multiple hydrogen bonds between the oxygen atoms to Ar–H, C–H, and the acidic methyl group create the CH/π interactions within the cavity.



1 : R = $C_{11}H_{23}$
2 : R = *i*-Bu
3 : R = $C_{11}H_{23}$
4 : R = *i*-Bu

Fig. 1. Calix[4]resorcinarene cavitands (**1**-**4**).

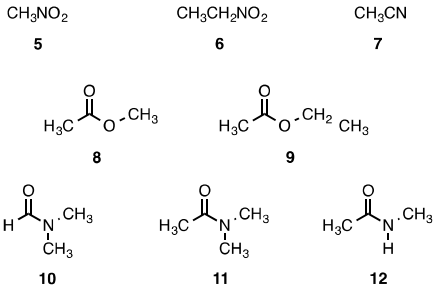
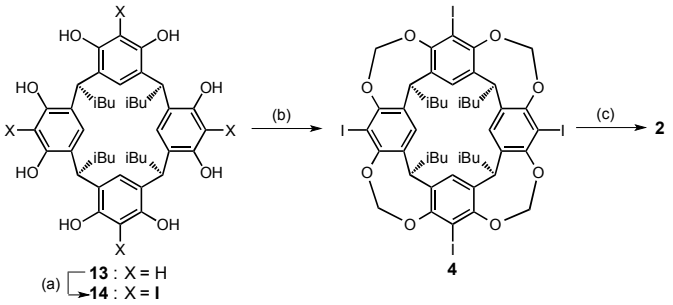


Fig. 2. Organic molecules **5**-**12** used in this study.

Results and discussion

Synthesis

Cavitand **1** was prepared by the reported procedure.[4a] Cavitand **2** was synthesized for the preparation of the single crystal (Scheme 1). *C*-isobutylresorcinarene **13** was prepared by a reported procedure.[7] Reaction of **13** with iodine afforded **14** in 17% yield. The Suzuki coupling reaction of **14** with bipyridine **15** gave **2** in 63% yield.



Scheme 1. Synthesis of **2**. Reagents and conditions: (a) water-Et_2O (1:1), rt, $NaHCO_3$, I_2, **13**, 17%, (b) DMF, 85 ˚C, CH_2BrCl, 26%, (c) $CsCO_3$, $PdCl_2(PPh_3)_2$, $AsPh_3$, 5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,2'-bipyridine (**15**), 1,4-dioxane, 120 ˚C, 63%.

Host-guest complexation

Standard titration experiments were carried out using ^{1}H NMR spectroscopy. The binding constants of guests **5**–**12** were examined in chloroform-d_1. Fig. 3 displays the ^{1}H NMR spectral changes of **5** upon the addition of **1**. The methyl resonance was observed at 4.33 ppm. When cavitand **1** was added to the guest solution, the methyl signal shifted upfield, indicating that the methyl protons experienced a large shielding effect that placed **5** deep inside the cavity where it was surrounded by the four aromatic rings of the resorcinarene. The four 2,2'-bipyridyl pillars significantly influenced the intermolecular association between **1** and **5**. The synthetic intermediate **3** did not bind to **5**, and the effective binding pocket of **1** was expanded by the presence of the simple bipyridyl pillars.

A 1:1 stoichiometry of the complex between cavitand **1** and guest **5** was determined using Job's plot. Plots of the chemical shift changes of the guest protons versus the concentrations of **1** gave a hyperbolic curve (Fig. 4a). A Gauss-Newton algorithm was used to analyze the non-linear curve fitting for the complexation-induced shifts (CIS) of the methyl protons, resulting in the association constant (Ka = 117 ± 5 L mol^{-1}) (Fig. 4b). The association constants of guests **6**–**12** with cavitand **1** were determined in the same manner with the estimated CIS values of the guest protons (Table 1).

Selective recognition was observed in a series of the guests. Cavitand **1** preferred to bind the guests possessing an acidic methyl group; for example, **5**, **7**, **8**, **9**, and **12** were encapsulated while the non-acidic methyl group of **6** and the absence of the methyl substituent for **10** did not facilitate any host-guest complexation. In addition, cavitand **1** did not encapsulate **11**, an analog of **12**, which possesses two methyl groups on the amide nitrogen atom. These findings implied that the CH/π interaction between the methyl group and the π-basic cavity drove the intermolecular association, indicating that the subtle changes in the guest shapes significantly influence the host-guest complexation.

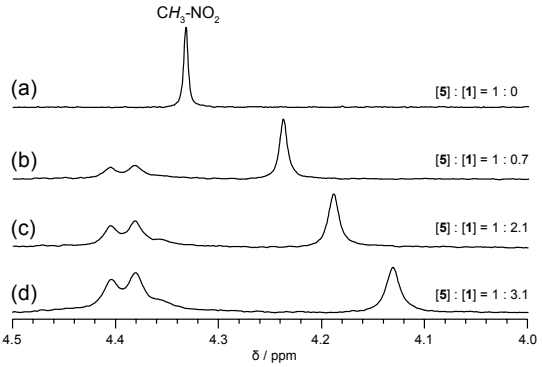


Fig. 3. Selected region of ^{1}H NMR spectra (300 MHz, chloroform-d_1, 293 K) of (a) **5**, (b) **5** + **1** ([**5**]:[**1**] = 1:0.7), (c) **5** + **1** ([**5**]:[**1**] = 1:2.1), and (d) **5** + **1** ([**5**]:[**1**] = 1:3.1). [**5**] = 1.0 mM.

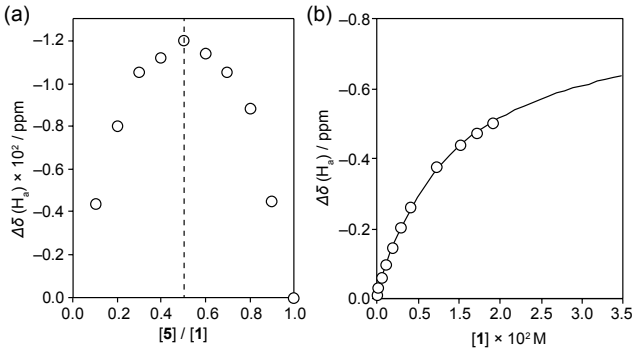


Fig. 4. (a) Job plot of **5** and (b) titration plot and curve-fitting of **5** (293 K, chloroform-d_1). In (b), the concentration of **5** was 1.0 mM throughout the experiment.

Table 1. Association constants (K_a) and complexation-induced chemical shift changes ($\Delta\delta$) of **5**-**12** for **1**. [a]

Guest	K_a / M^{-1}	$\Delta\delta$ / ppm [b]
5	117 ± 5	–0.82
6	not bound [c]	-
7	80 ± 1	–0.23
8	68 ± 3	–0.23 (CH_3CO), –0.21 (CH_3O)
9	74 ± 7	–0.28
10	not bound [c]	-
11	not bound [c]	-
12	50 ± 10	–0.05

[a] Every titration experiment was carried out in chloroform-d_1 at 293 K. [b] $\Delta\delta$ = δ (bound guest) – δ (free guest). δ (bound guest) was estimated by the non-linear least square fitting of the titration data. [c] Host-guest complexation was not observed under these conditions.

The CIS values of the methyl groups provide information about complex structures because the shielding region is mainly produced within the cavity. The methyl groups of **7**, **8**, and **9** displayed the estimated CIS values of approximately –0.2 ppm, whereas the methyl group of **12** showed a smaller CIS value of –0.05 ppm, suggesting a shallow placement of **12** in the cavity. This finding explains the weaker binding of **12** to the cavity because the methyl group cannot create enough contacts with the four aromatic rings, which are responsible for attractive CH/π interactions. By contrast, the CIS value of **5** was clearly larger than those observed for the other guests, placing **5** deeper in the cavity. The closer contacts between the methyl group and the aromatic rings indicate that the complex likely receives more attractive CH/π interactions, leading to the largest association constant.

A unique binding mode was found for the complexations of acetates **8** and **9**. Both acetates bound into the cavity with fairly large association constants. Fig. 5a and b displayed the ^{1}H NMR spectra of **8** and **9** in the absence and presence of 3.0 equivalent of **1**, respectively. The acetyl methyl groups of **8** and **9** displayed upfield shifts in the presence of **1**. The ethoxy group of **9** remained unchanged, whereas the methoxy group of **8** was shifted upfield. These CIS values indicated the difference in the conformational characteristics of the host-guest complexes. Guest **9** stayed within the cavity while the acetyl methyl group pointed down into it. By contrast, **8** adopted two conformations: one brings the acetyl methyl group closer to the cavity, and the other places the methoxy groups deep inside the cavity even though the methoxy protons are not acidic.

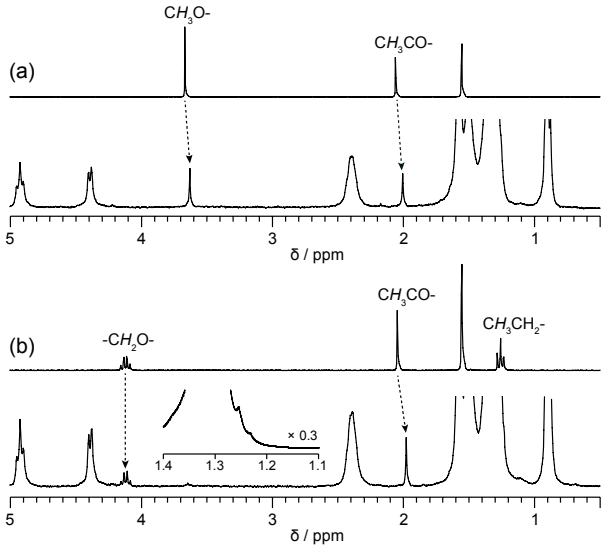


Fig. 5. ^{1}H NMR spectra (300 MHz, chloroform-d_1, 293 K) of (a) **8** and (b) **9** before and after the addition of 3.0 equivalents of **1**. [**8**] = [**9**] = 1.0 mM.

Molecular modeling study

Molecular mechanics calculations of the host-guest complexes gave structural insights into the steric interactions that drove guest selection. The calculations for the host-guest complexes were carried out using MacroModel V. 9.1 with an MMFF force field.[8] To reduce the conformational options of the host-guest complexes, cavitand **16** was used instead of cavitand **1** and the four long alkyl feet of **16** were replaced with methyl groups. All possible geometries of the host-guest complexes of cavitand **16** with guests **5**–**12** except for **10** were evaluated. The energy-minimized structures of cavitand **16** and the host-guest complexes are shown in Fig. 6a-h. The 2,2'-bipyridyl pillars of **16** generated the bottle neck cavity that permitted one methyl group to remain accessible. The acidic methyl groups were positioned as the pseudo C_3 axes in the cavity which, along with the C_4 axis of the cavitand, created close van der Waals contacts with the aromatic rings. By contrast, **11** was tilted due to the steric interactions with the cavity portal.

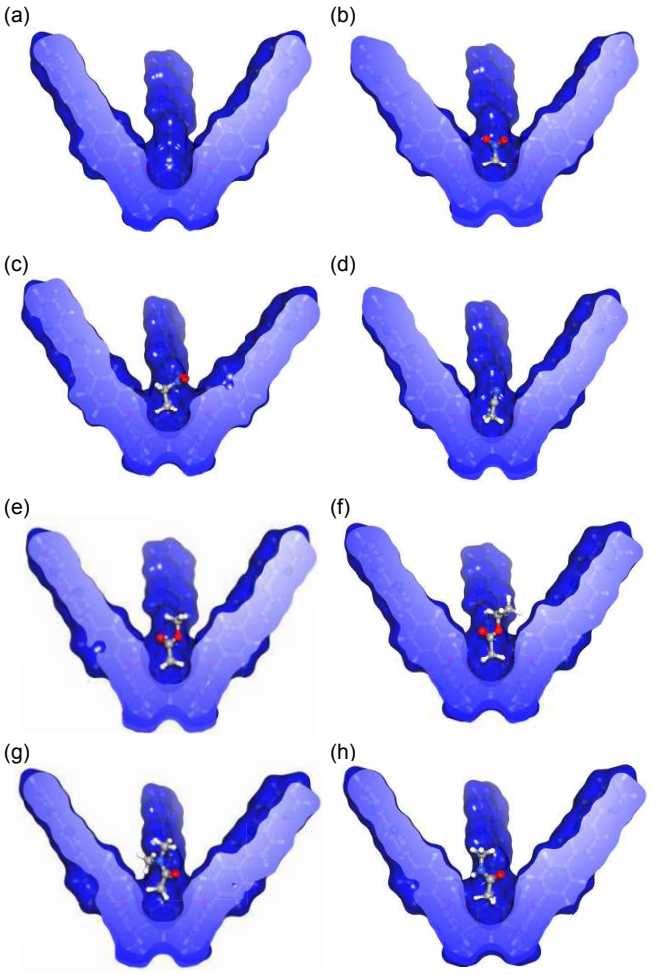
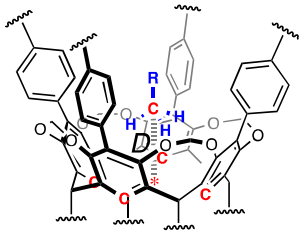


Fig. 6. Energy-minimized structures of (a) **16**, (b) **5**⊂**16**, (c) **6**⊂**16**, (d) **7**⊂**16**, (e) **8**⊂**16**, (f) **9**⊂**16**, (g) **11**⊂**16**, and (h) **12**⊂**16**. Color scheme: gray (carbon), white (hydrogen), red (oxygen).



R	*D* / Å
-NO_2	2.93
-CH_2NO_2	3.38
-CN	2.88
-COOMe	3.13
-COOEt	3.21
$CONMe_2$	4.03
CONHMe	3.34

Fig. 7. Schematic representation of the complex structure of a guest. The centroid of four carbon atoms C25, C26, C27, C28 is denoted by "*". The inter-atomic distance (*D*) between the guest methyl carbon and the cavity center is depicted by a dashed line.

To discuss the steric interactions between the four aromatic rings of the cavity and the guest methyl groups, the distances (*D*) between the guest methyl carbons and the centroid of the four carbon atoms of the cavitands (C25, C26, C27, C28) were determined on the basis of the calculated structures (Fig. 7). The *D* values were sensitive to the molecular structures of the guests. The thread-like shapes of **5** and **7** allowed them to stay deeper inside the cavity, resulting in closer orientations that generated the effective CH/π interactions. By contrast, the other guests were more shallowly positioned, with *D* values of more than 3.1 Å. Accordingly, expansions in the molecular structures most likely increased the unfavorable steric interactions with the cavity portal. For example, **12** stayed deeper inside the cavity than **11** did (*D*: 4.03 Å for **11** and 3.34 Å for **12**).

The association constants were fairly correlated with the distances. Although **5** demonstrated the highest association constant, the *D* value was close to that of **7**. A nitro group has two negatively charged oxygen atoms that are capable of generating hydrogen bonds with many hydrogen bonding donor functionalities even though these interactions are weak. The calculated structure illustrated that the Ar–H bonds were directed to the oxygen atoms of the nitro group, implying the presence of Ar–H···O hydrogen bonds. However, the molecular mechanics calculations could not provide quantitative evaluations of such weak noncovalent interactions. Thus, the given structure might not have reproduced a difference in the structure arising from the weak interactions.

Table 2. Crystallographic parameters of $\mathbf{5}_2\subset\mathbf{2}_2$ and **4**

Crystal system	Tetragonal	Monoclinic
Space group	*P*4/*nnc* (#126)	*C*2/*m* (#12)
Formula [a]	$C_{113}H_{99}N_9O_{10}$	$C_{48}H_{52}O_8I_4$
Formula weight [a]	1743.01	1264.5
a /Å	19.221(3)	25.752(6)
b /Å	19.221(3)	14.426(3)
c /Å	26.996(4)	19.859(5)
α / °	90	90
β / °	90	123.395(2)
γ / °	90	90
V /Å^3	9973.9(2)	6159(2)
Z	4	4
Density /g cm^{-3} [a]	1.16	2.73
Temperature /*K*	123	123
Crystal size / mm^3	0.21 × 0.16 × 0.15	0.25 × 0.06 × 0.06
# of reflections	81727	17086
# of unique reflections	3995	7751
R_{int}	0.0359	0.0380
# of observed reflections	3440	6324
# of parameters.	307	285
*R*1	0.0984	0.0544
*wR*2	0.2778	0.1477
G.O.F.	1.072	1.086
CCDC	1024890	1024891

[a] Formula, Formula weight, and density were known constants only.

Host-guest complex in the solid state

Single crystals of the host-guest complex of **2** with **5** were obtained from a chloroform solution containing **2** and **5** by slow evaporation of the solvent at room temperature.[9] Colorless crystals of $\mathbf{5}_2\subset\mathbf{2}_2$ were crystallized in the tetragonal crystal system with the space group *P*4/*nnc* (#126).† The crystallographic parameters are compiled in Table 2. The asymmetric unit contained a quarter of **2**. The crystallographically imposed C_4-rotational axis penetrated the center of **2**. Guest **5** lay on the C_4-rotational axis and was disordered over four positions. Cavitand **2** dimerized to form chiral capsule $\mathbf{2}_2$ with a *P*- or *M*-helical structure. Fig. 8a shows the front and top views of $\mathbf{2}_2$ with the *M*-helical structure. The 2,2'-bipyridyl pillars resulted in π-π stacking interactions that generated the chiral capsular structure. The crystal packing of $\mathbf{5}_2\subset\mathbf{2}_2$ displayed the racemic crystal system with $Z = 4$, which contained one pair of the enantiomers in the unit cell (Fig. 8b). Single crystals of **4** were successfully prepared from a mixed solution of nitromethane and dichloromethane. X-ray diffraction analysis revealed that the crystal belonged to the monoclinic crystal system with the space group *C*2/*m* (#12).† The crystallographic parameters are listed in Table 2.

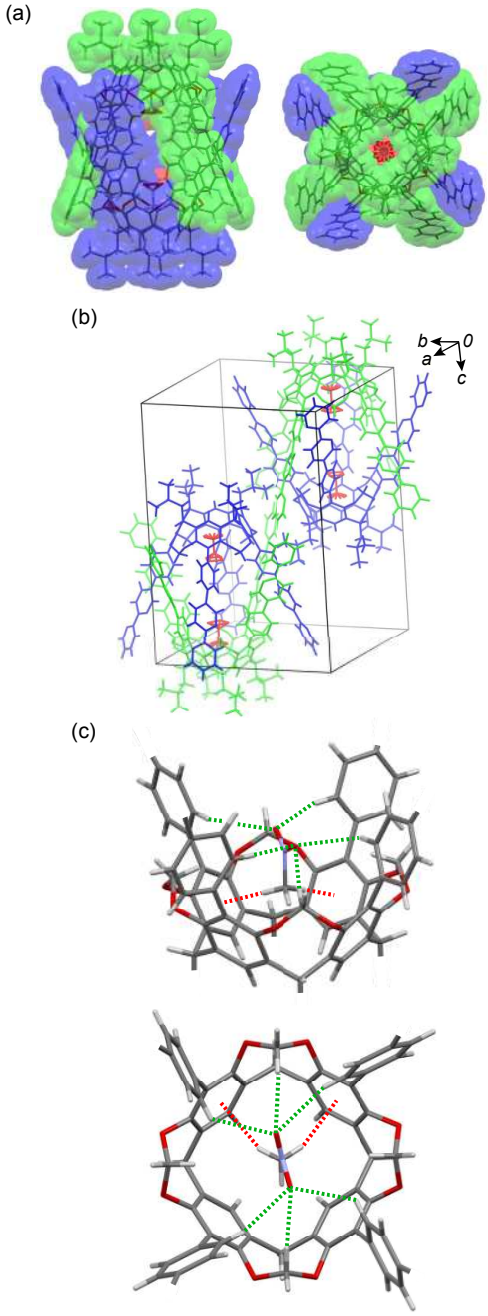


Fig. 8 (a) Front and top views of the X-ray crystal structure of $\mathbf{5}_2\subset\mathbf{2}_2$ showing an *M*-helical structure. (b) Crystal packing of $\mathbf{5}_2\subset\mathbf{2}_2$. Color scheme: blue and green (**2**), and red (**5**). Guest **5** is disordered over four positions. NOTE: The diffuse electron density arising from the disordered and unidentified moieties was

treated with the SQUEEZE routine within the PLATON software package.[10] (c) the front and top views of **5** in the cavity of **2**. Only one of the four disordered guests is shown. The red and the green dotted lines denote the C–H/π interaction and C–H···O hydrogen bonding, respectively.

The capsular structure $\mathbf{2}_2$ captured two nitromethane molecules at each end of the cavity. The methyl group of **5** was positioned deep inside the cavity of resorcinarene, facing the four aromatic rings with a *D* value of 2.495 Å (Fig. 8c). Small guests such as the methyl groups of acetonitrile and ethyl acetate were commonly found at the cavity of the cavitands, and the optimum *D* value was approximately 2.8–3.3 Å.[11] In the crystal, the four bridge methylene C–H bonds and the four Ar–H bonds were directed toward the oxygen atoms of the nitro group, most likely forming the trifurcate C–H···O hydrogen bond (Fig. 8c). These multiple hydrogen bonds most likely enforced the deep placement of the methyl group inside the cavity, explaining the unusually short *D* and the large CIS values. In fact, the absence of the 2,2'-bipyridyl pillars resulted in the highly disordered orientation of the guest within the cavity; for instance, guest **5** was not precisely located within the cavity. With the aid of some weak hydrogen bonding interactions, the four 2,2'-bipyridyl pillars played a crucial role in defining the guest orientation.

Conclusions

In conclusion, the calix[4]resorcinarene-based cavitand **1** contained four 2,2'-bipyridyl pillars and could encapsulate nitromethane **5**, acetonitrile **7**, methyl acetate **8**, ethyl acetate **9**, and *N*-methylacetamide **12** to form 1:1 host-guest complexes. By contrast, cavitand **1** showed no affinity for nitroethane **6**, *N*,*N*-dimethylformamide **10**, or *N*,*N*-dimethylacetamide **11**. Differences in the molecular structures of the guests greatly influenced the guest selection by the cavity. Molecular mechanics calculations and X-ray diffraction analyses revealed that the steric requirements of the 2,2'-bipyridyl pillars allowed for the capture of a methyl group within the π-basic cavity. CH/π interactions between the methyl group and the four aromatic rings were fairly well correlated with the acidity of the guest methyl groups. In the solid state, the π-π stacking of the flat bipyridyl rings of cavitand **2** induced the formation of the dimeric capsule, which encapsulated two molecules of **5**. In the solid state, the multiple hydrogen bonds between the nitro group, Ar–H, and C–H were explained by the unusually short distance *D* compared to those found in previous cavitand complexes with guests.

Experimental

General

All chemicals and solvents were purchased from Kanto Chemical Co., Ltd., Wako Pure Chemical Co., Ltd., Tokyo Kasei Kogyo Co., Ltd., and Sigma-Aldrich Co., Ltd. and were used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a VARIAN 300 MHz spectrometer. Chemical shifts are quoted as parts per million (ppm) relative to chloroform (chloroform-d_1, δ = 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C; dimethylsulfoxide-d_6, δ = 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C). High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific LTQ Orbitrap XL by electron splay ionization (ESI). Melting points were measured with a Yanagimoto micro melting point apparatus and uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400CHN elemental analyzer.

X-ray Crystallography

X-ray crystallographic data of $\mathbf{5}_2\subset\mathbf{2}_2$ and **4** were collected on a Bruker SMART AEPX II ULTRA CCD diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) at 123 K. The crystal structures were solved using the direct method with the SHELXS-2013 program and refined by successive differential Fourier syntheses and full-matrix least-squares procedures using SHELXL-2013.[12] Anisotropic thermal factors were applied to all non-hydrogen atoms. The hydrogen atoms were generated geometrically. The 2,2'-bipyridyl moiety was disordered over two positions and the restraint was applied to the rings. The diffuse electron density arising from the disordered and unidentified moieties found in $\mathbf{5}_2\subset\mathbf{2}_2$ and **4** were treated with the SQUEEZE routine in the PLATON software package.[10] CCDC numbers are 1024890 for $\mathbf{5}_2\subset\mathbf{2}_2$ and 1024891 for **4** and contain the supplementary crystallographic data for this paper.

Synthesis of 14

To a solution of **13** (20.03 g, 28.10 mmol) in water and ether (1:1), sodium hydrogen carbonate (9.45 g, 113 mmol) and iodine (28.6 g, 113 mmol) were added at room temperature under argon atmosphere. The solution was stirred for 24 h at room temperature. A precipitate was filtered off and solid residue was washed with cold acetone and dichloromethane for several times to afford **14** as a yellow solid (5.80 g, 17%). m.p. > 300 ºC, ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6): δ 9.36 (s, 8H), 7.48 (s, 4H), 4.43 (t, 4H, J = 7.7 Hz), 2.16 (m, 8H), 1.34 (m, 4H), 0.92 (d, 24H, J = 6.6 Hz); ^{13}C NMR (75 MHz, dimethylsulfoxide-d_6): δ 150.86, 126.25, 124.76, 81.39, 42.05, 33.92, 26.03, 22.73; HRMS (ESI–): calcd for $C_{44}H_{51}O_8I_4$ m/z 1214.9768; found m/z 1214.9764 $[M–H]^-$.

Synthesis of 4

To a solution of **14** (4.00 g, 3.29 mmol) in dry DMF (50 mL), bromochloromethane (8.60 mL, 131 mmol) and potassium carbonate (3.64 g, 26.3 mmol) were added at room temperature under a nitrogen atmosphere. The solution was stirred for 3 h at 85 ºC. The mixture was allowed to cool to room temperature. The reaction was quenched with 2 M aqueous hydrogen chloride. The organic layer was separated with ethyl acetate, washed with brine, and dried over sodium sulfonate. The solvent was removed at reduced pressure. The organic residue was purified by chromatography on a silica gel (5% ethyl acetate–hexane) to afford **4** as a white solid (0.89 g, 26%). m.p. > 300 ºC, ^{1}H NMR (300 MHz, chloroform-d_1): δ 7.06 (s, 4H), 5.98 (d, 4H, J = 7.4 Hz), 4.99 (t, 4H, J = 8.1 Hz), 4.32 (d, 4H, J = 7.4 Hz), 2.08 (t, 8H, J = 7.5 Hz), 1.53 (m, 4H), 1.01 (d, 24H, J = 6.6 Hz); ^{13}C NMR (75 MHz, chloroform-d_1): δ 154.97, 138.86, 121.13, 98.86, 93.12, 39.09, 35.92, 26.21, 22.98; HRMS (ESI+): calcd for $C_{48}H_{52}O_8I_4$ m/z 1263.9835; found m/z 1263.9843 $[M]^+$.

Synthesis of 2

To a stirred solution of **4** (183 mg, 1.45×10^{-1} mmol), palladium bis(triphenylphosphine) dichloride (50.0 mg, 7.25×10^{-3} mmol) and cesium carbonate (1.41 g, 4.35 mmol) in 1,4-dioxane (25 mL), 5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,2'-bipyridine **15** (520 mg, 1.45 mmol), and triphenylarsine (177 mg, 5.78×10^{-1} mmol) in 1,4-dioxane (40 mL) was added at room temperature. The solution was refluxed for 1 h. The solution was allowed to cool to room temperature and was filtered with celite. The filtrate was concentrated under reduced pressure. The organic residue was purified by gel permeation chromatography (chloroform) to afford cavitand **2** as a pale yellow solid (162 mg, 63%). m.p. > 300 ºC, ^{1}H NMR (300 MHz, chloroform-d_1): δ 8.94 (s, 4H), 8.64 (d, 4H, J = 3.9 Hz), 8.54 (d, 4H, J = 7.8 Hz), 8.51 (d, 4H, J = 7.8 Hz), 8.06 (d,

4H, J = 8.3 Hz), 7.89 (t, 4H, J = 7.8 Hz), 7.64 (d, 8H, J = 7.8 Hz), 7.42 (s, 4H), 7.31 (m, 4H), 7.22 (d, 8H, J = 7.8 Hz), 5.41 (d, 4H, J = 6.9 Hz), 5.09 (t, 4H, J = 9.0 Hz), 4.39 (d, 4H, J = 6.9 Hz), 2.30 (t, 8H, J = 7.4 Hz), 1.73 (m, 4H), 1.12 (d, 24H, J = 6.5 Hz); ^{13}C NMR (75 MHz, chloroform-d_1): δ 155.86, 155.02, 152.78, 149.26, 147.61, 138.71, 137.13, 136.41, 135.98, 135.21, 133.95, 130.94, 128.87, 126.67, 123.78, 121.24, 121.19, 120.58, 100.74, 39.54, 35.07, 26.36, 23.14; HRMS (ESI+): calcd for $C_{112}H_{98}N_8O_8$ m/z 841.3748; found m/z 841.3760 $[M + 2H]^+$.

Acknowledgements

This work was supported by Grant-in-Aids for Scientific Research (B) (No. 21350066) and Challenging Exploratory Research (No. 21355105) of JSPS as well as by Grant-in-Aids for Scientific Research on Innovative Areas, "Stimuli-responsive Chemical Species for the Creation of Functional Molecules" and "New Polymeric Materials Based on Element-Blocks" (No. 25109529, 25102532).

Notes and references

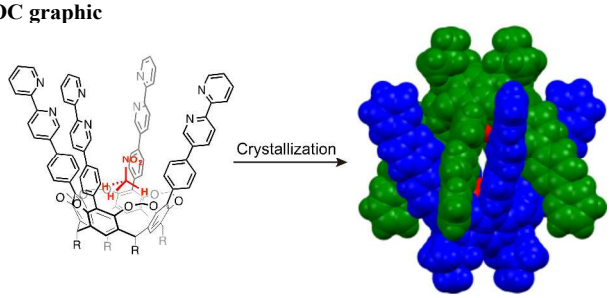
Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima, 739-8526 Japan

haino@hiroshima-u.ac.jp

Electronic Supplementary Information (ESI) and crystallographic information files (CIFs) are available at DOI: 10.1039/b000000x/

1. (a) D. J. Cram and J. M. Cram, *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, UK, 1994; (b) C. D. Gutsche, *Calixarene: An Introduction*, Royal Society of Chemistry, Cambridge, UK, 2008; (c) J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, A John Wiley and Sons, 2009.
2. (a) D. J. Cram, S. Karbach, H.-E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson and R. C. Helgeson, *J. Am. Chem. Soc.*, 1988, **110**, 2229-2237; (b) E. Kalenius, D. Moiani, E. Dalcanale and P. Vainiotalo, *Chem. Commun.*, 2007, 3865-3867; (c) M. Melegari, M. Suman, L. Pirondini, D. Moiani, C. Massera, F. Ugozzoli, E. Kalenius, P. Vainiotalo, J.-C. Mulatier, J.-P. Dutasta and E. Dalcanale, *Chem.-Eur. J.*, 2008, **14**, 5772-5779; (d) R. M. Yebeutchou and E. Dalcanale, *J. Am. Chem. Soc.*, 2009, **131**, 2452-2453; (e) E. Biavardi, C. Tudisco, F. Maffei, A. Motta, C. Massera, G. G. Condorelli and E. Dalcanale, *Proc. Natl. Acad. Sci. USA*, 2012, **109**, 2263-2268.
3. (a) K. D. Shimizu and J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA*, 1995, **92**, 12403-12407; (b) R. K. Castellano, D. M. Rudkevich and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1996, **118**, 10002-10003; (c) B. C. Hamann, K. D. Shimizu and J. Rebek, Jr., *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 1326-1329; (d) L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469-472; (e) T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 1998, **394**, 764-766; (f) F. C. Tucci, D. M. Rudkevich and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 4928-4929; (g) K. Kobayashi, T. Shirasaka, K. Yamaguchi, S. Sakamoto, E. Horn and N. Furukawa, *Chem. Commun.*, 2000, 41-42; (h) L. R. MacGillivray, P. R. Diamente, J. L. Reid and J. A. Ripmeester, *Chem. Commun.*, 2000, 359-360; (i) F. Fochi, P. Jacopozzi, E. Wegelius, K. Rissanen, P. Cozzini, E. Marastoni, E. Fisicaro, P. Manini, R. Fokkens and E. Dalcanale, *J. Am. Chem. Soc.*, 2001, **123**, 7539-7552; (j) K. Kobayashi, K. Ishii, S. Sakamoto, T. Shirasaka and K. Yamaguchi, *J. Am. Chem. Soc.*, 2003, **125**, 10615-10624; (k) D. Ajami and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2006, **128**, 5314-5315.
4. (a) T. Haino, M. Kobayashi, M. Chikaraishi and Y. Fukazawa, *Chem. Commun.*, 2005, 2321-2323; (b) T. Haino, M. Kobayashi and Y. Fukazawa, *Chem.-Eur. J.*, 2006, **12**, 3310-3319; (c) T. Haino, K. Fukuta, H. Iwamoto and S. Iwata, *Chem.-Eur. J.*, 2009, **15**, 13286-13290; (d) Y. Tsunoda, K. Fukuta, T. Imamura, R. Sekiya, T. Furuyama, N. Kobayashi and T. Haino, *Angew. Chem. Int. Ed.*, 2014, **53**, 7243-7247.
5. T. Haino, H. Shio, R. Takano and Y. Fukazawa, *Chem. Commun.*, 2009, 2481-2483.
6. (a) R. Sekiya, Y. Yamasaki, S. Katayama, H. Shio and T. Haino, *CrystEngComm*, 2013, **15**, 8404-8407; (b) R. Sekiya, Y. Yamasaki, W. Tada, H. Shio and T. Haino, *CrystEngComm*, 2014, **16**, 6023-6032.
7. L. Abis, E. Dalcanale, A. Du vosel and S. Spera, *J. Org. Chem.*, 1988, **53**, 5475-5479.
8. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440-467.
9. Single crystals, obtained from a chloroform solution of **2**, became opaque immediately after removal from the mother liquor. The stable single crystals were obtained only in the presence of nitromethane. This implies that the guest encapsulation might stabilize the dimeric structure of $\mathbf{5}_2\subset\mathbf{2}_2$ in the solid state.
10. A. L. Spek, *Acta Crystallogr. Sect. D: Biol. Crystallogr.*, 2009, **65**, 148-155.
11. (a) R. Pinalli, F. F. Nachtigall, F. Ugozzoli and E. Dalcanale, *Angew. Chem. Int. Ed.*, 1999, **38**, 2377-2380; (b) E. S. Barrett, J. L. Irwin, P. Turner and M. S. Sherburn, *J. Org. Chem.*, 2001, **66**, 8227-8229; (c) V. A. Azov, P. J. Skinner, Y. Yamakoshi, P. Seiler, V. Gramlich and F. Diederich, *Helv. Chim. Acta*, 2003, **86**, 3648-3670; (d) L. Pirondini, G. Vecchi, S. Negri, A. Di Blasi, C. Massera and E. Dalcanale, *Collect. Czech. Chem. Commun.*, 2004, **69**, 1362-1380; (e) C. B. Aakeröy, N. Schultheiss and J. Desper, *CrystEngComm*, 2006, **8**, 502-506; (f) C. B. Aakeröy, N. Schultheiss and J. Desper, *Org. Lett.*, 2006, **8**, 2607-2610; (g) E. Menozzi, M. Busi, C. Massera, F. Ugozzoli, D. Zuccaccia, A. Macchioni and E. Dalcanale, *J. Org. Chem.*, 2006, **71**, 2617-2624; (h) A. Yoshida, K. Goto and T. Kawashima, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 793-795; (i) C. Aakeröy, N. Schultheiss and J. Desper, *CrystEngComm*, 2007, **9**, 211-214; (j) M. G. Mc Kay, H. B. Friedrich and G. E. M. Maguire, *Acta. Crystallogr. Sect. E: Struct. Report*, 2008, **64**, O98; (k) K. Salorinne and M. Nissinen, *CrystEngComm*, 2009, **11**, 1572-1578; (l) G. Wagner, V. B. Arion, L. Brecker, C. Krantz, J.-L. Mieusset and U. H. Brinker, *Org. Lett.*, 2009, **11**, 3056-3058; (m) H. El Moll, D. Sémeril, D. Matt and L. Toupet, *Eur. J. Org. Chem.*, 2010, 1158-1168; (n) N. Şahin, D. Sømeril, E. Brenner, D. Matt, I. Özdemir, C. Kaya and L. Toupet, *ChemCatChem*, 2013, **5**, 1116-1125.
12. G. M. Sheldrick, *Acta crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112-122.

TOC graphic



Calix[4]resorcinarene-based cavitand recognized the methyl group of the guests to form 1:1 host-guest complexes. In the solid state, cavitand formed a dimeric capsule in which two molecules of nitromethane were entrapped by CH/π interactions and C–H···O hydrogen bonding.