Tetrahedron 65 (2009) 7234–7239

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Guest-encapsulation behavior in a self-assembled heterodimeric capsule

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ARTICLE INFO

Article history:
Received 2 September 2008
Received in revised form 7 October 2008
Accepted 27 November 2008
Available online 3 December 2008

Keywords:
Cavitand
Self-assembly
Capsule
Molecular recognition
Encapsulation

ABSTRACT

Tetra(4-pyridyl)-cavitand **1** and tetrakis(4-hydroxyphenyl)-cavitand **2** self-assemble into a heterodimeric capsule **1**·**2** via four PhOH···pyridyl hydrogen bonds in $CDCl_3$, wherein one molecule of 1,4-disubstituted-benzene as a guest is encapsulated to form a ternary complex, guest@(**1**·**2**). The X-ray crystallographic analysis of (methyl *p*-ethoxybenzoate)@(**1**·**2**) confirmed that the methyl ester and ethoxy groups of the encapsulated guest are oriented to the cavity ends of the **1** and **2** units, respectively. The scope and limitation of guest encapsulation in **1**·**2**, including guest-binding selectivity and orientational isomeric selectivity, are described from the viewpoint of size complementarity and CH–π, CH–halogen, and halogen–π interactions between guest and the cavity of **1**·**2**.

1. Introduction

Carcerands and hemicarcerands, in which two calix[4]resorcinarene cavitands are held together by four covalent linkages, have been developed by Cram and others.[1] They have attracted considerable attention from the viewpoint of stabilization of reactive intermediates and microvesicles for drug delivery by the confinement of guest molecules inside the capsules away from bulk phases.[1] Error correction through thermodynamic equilibration, minimization of synthetic effort by use of modular subunits, and control of assembly processes through subunit design are characteristics of supramolecular approaches to self-assembly. On the basis of this concept, cavitand-based capsules have been constructed under thermodynamic control using noncovalent interactions such as hydrogen bonds,[2] metal-coordination bonds,[3] ionic interactions,[4] and solvophobic interactions,[5] and using reversible dynamic covalent bonds.[6]

Stereoisomerism upon guest(s) encapsulation in self-assembling capsules offers a new concept in physical organic chemistry as well as supramolecular chemistry.[7] Heterodimeric capsules provide an unsymmetrical nanospace.[8,9] Orientational isomerism emerges from the encapsulation of an unsymmetrical guest in a heterodimeric capsule,[10,11] which may endow a heterodimeric capsule with potential as a building block for molecular devices.[7,12] Recently, we have reported the self-assembly of tetra(4-pyridyl)-cavitand **1** and tetrakis(4-hydroxyphenyl)-cavitand **2** into a heterodimeric capsule **1**·**2** in a rim-to-rim fashion via four PhOH···pyridyl hydrogen bonds, wherein one molecule of 1,4-disubstituted-benzene as a guest is encapsulated to form a ternary complex, guest@(**1**·**2**), and the exchange of guest in and out of **1**·**2** is very slow on the NMR time scale (Scheme 1a).[13] It is noted that **1**·**2** expresses the orientational isomerism of an encapsulated unsymmetrical guest with high orientational isomeric selectivity because the electronic environment of the **1** unit is different from that of the **2** unit (Scheme 1b).[13] Here we report the X-ray crystal structure of (methyl 4-ethoxybenzoate)@(**1**·**2**) and the scope and limitation of guest encapsulation in **1**·**2**, including guest-binding selectivity and orientational isomeric selectivity.

2. Results and discussion

2.1. X-ray crystal structure of (methyl 4-ethoxybenzoate)@(1b·2b)

Single crystals of methyl 4-ethoxybenzoate-encapsulating heterodimeric capsule, **5**@(**1b**·**2b**), suitable for X-ray diffraction analysis were obtained by slow diffusion of benzene into a $CHCl_3$ solution of a 1:1:3 mixture of tetra(4-pyridyl)-cavitand **1b**, tetrakis(4-hydroxyphenyl)-cavitand **2b** (R=$CH_2CH(CH_3)_2$), and methyl 4-ethoxybenzoate **5**.[14] As shown in Figure 1, cavitands **1b** and **2b**

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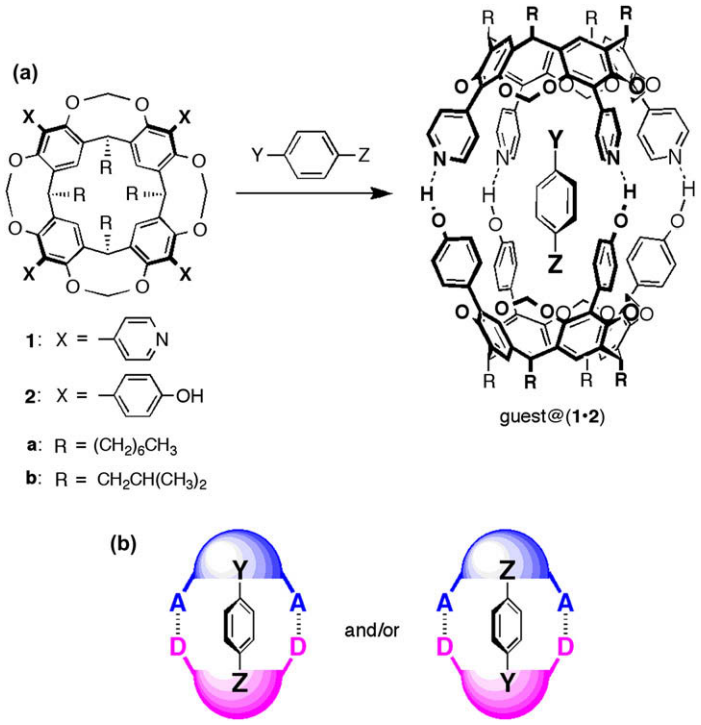
doi:10.1016/j.tet.2008.11.093



Scheme 1. (a) Self-assembly of tetra(4-pyridyl)-cavitand **1** and tetrakis(4-hydroxyphenyl)-cavitand **2** into a heterodimeric capsule **1**·**2** and guest encapsulation. (b) Orientational isomerism of an unsymmetrical guest within a heterodimeric capsule.

self-assemble into the heterodimeric capsule **1b**·**2b** in a rim-to-rim fashion via four PhOH···pyridyl hydrogen bonds with the O···N distances of 2.67–2.79 Å. The **1b**·**2b** possesses an inner cavity of the approximate dimensions 4.8×15.3 Å and four equatorial portals of ca. 2.4×5.9 Å (including van der Waals radii).[15] Exactly one molecule of **5** is encapsulated in the cavity of **1b**·**2b**, and oriented with the long axis of the guest along the long axis of **1b**·**2b** so as to maximize guest–capsule CH–π interaction. The methyl ester and ethoxy groups of the encapsulated **5** are oriented to the cavity ends of the **1b** and **2b** units, respectively. This orientation is in good agreement with that determined previously by the ^{1}H NMR study.[13]

The close contact distances between guest-CH_3 and the aromatic cavity of host are 2.64 and 2.88 Å for the CO_2CH_3···Cπ–**1b**, and 2.73 and 2.86 Å for the OCH_2CH_3···Cπ–**2b**, indicating guest–capsule CH–π interaction.[11b,16] The carbonyl oxygen atom of the CO_2CH_3 group interacts with an inner proton of the methylene-bridge rim (O–$CH_{in}H_{out}$–O) of the **1b** unit with the C═O···H_{in}C distance of 2.27 Å.[17] There is also weak C═O···HC interaction of the carbonyl oxygen atom with a *p*-pyridyl β-proton of the **1b** unit (2.37 and 2.61 Å). There is no interaction between the oxygen atom of the ethoxy group and a *p*-phenol β-proton of the **2b** unit (2.95 and 3.02 Å).

The heterodimeric capsule **1b**·**2b** possesses four large equatorial portals, which are capped with two molecules of $CHCl_3$ and two molecules of benzene as recrystallization solvents in the crystal structure of **5**@(**1b**·**2b**), as shown in Figure 2. There are loose halogen–π interaction between the accommodated $CHCl_3$ and the benzene ring of the encapsulated **5** (Cl···Cπ distances of 3.57 and 3.68 Å) and CH–halogen interaction between $CHCl_3$ and the outer protons of the methylene-bridge rim (O–$CH_{in}H_{out}$–O) of **1b**·**2b** (Cl···H_{out}C distances of 2.65 and 2.74 Å).[11b,17,18] The accommodated benzene loosely interacts with the *p*-pyridyl and *p*-phenol groups of **1b**·**2b** in an edge-to-face π–π stacking fashion.

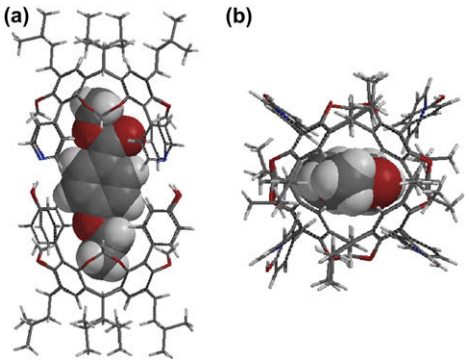


Figure 1. X-ray crystal structure of (methyl 4-ethoxybenzoate)@(**1b**·**2b**): (a) front view and (b) top view. Cocrystallization solvents are omitted for clarity.

2.2. NMR study for guest encapsulation in 1a·2a: scope and limitation

In the ^{1}H NMR study, **1a** and **2a** with side chains R=$(CH_2)_6CH_3$ were used.[13] Figure 3 shows the ^{1}H NMR spectra of a mixture of **1a**·**2a** (5 mM) and 1–15 equiv of 4,4′-dimethylbiphenyl **21** in $CDCl_3$ at 23 °C. Upon addition of **21** to **1a**·**2a**, a mixture of **21**@(**1a**·**2a**), guest-free **1a**·**2a**, and free **21** was observed, wherein the ^{1}H NMR signals of the three species independently appeared. This result indicates that exchanges between **21**@(**1a**·**2a**) and guest-free **1a**·**2a** and between **21**@(**1a**·**2a**) and free **21** are slow on the NMR time scale. The signals of guest-free **1a**·**2a** almost disappeared upon addition of 15 equiv of **21** (Fig. 3f). As the electronic environment of **1a** is different from that of **2a**, **21** encapsulated in **1a**·**2a** was desymmetrized, and its ^{1}H NMR signals appeared as two sets of singlet for the methyl protons with $\Delta\delta$ values ($\delta_{\text{encapsulated guest}}-\delta_{\text{free guest}}$) of −3.76 and −3.56 ppm and as two sets of doublet for the aromatic 3,3′-protons with $\Delta\delta$ of −1.00 and −0.82 ppm. These $\Delta\delta$ values clearly indicate that the methyl groups are oriented to both aromatic

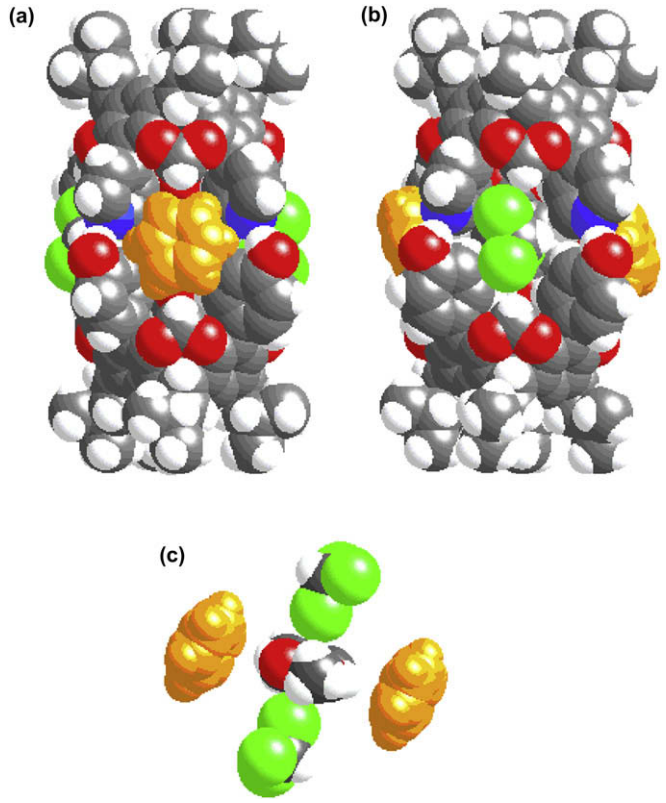


Figure 2. Space-filling representation of X-ray crystal structure of (methyl 4-ethoxybenzoate)@(**1b**·**2b**) with $CHCl_3$ and benzene molecules capping the equatorial portals of **1b**·**2b**: (a) front view and (b) side view. (c) Top view of the encapsulated guest, the capping $CHCl_3$, and benzenes. Benzene molecule and chlorine atom are shown in orange and green, respectively. Other cocrystallization solvents are omitted for clarity.

cavity ends of **1a**·**2a** and the guest does not tumble within **1a**·**2a** on the NMR time scale. Based on the ^{1}H NMR integration changes of signals of **21**@(**1a**·**2a**) as a function of the concentration of **21**, the association constant of heterodimeric capsule **1a**·**2a** with guest **21** was estimated to be $K_a=(2.76\pm0.05)\times10^2\ M^{-1}$ in $CDCl_3$ at 23 °C.

Under the conditions of [**1a**·**2a**]=[dimethyl terephthalate **11**]=5 mM, the ^{1}H NMR signals of guest-free **1a**·**2a** almost disappeared, namely, the association of **1a**·**2a** with **11** was much greater than that of **1a**·**2a** with **21**. Therefore, as shown in Figure 4, the dilution experiments of [**1a**·**2a**]=[**11**] in the range 0.5–2 mM were carried out to determine the association constant of $K_a=(2.02\pm0.13)\times10^4\ M^{-1}$ in $CDCl_3$ at 23 °C.[19] In the competitive encapsulation experiments, the ^{1}H NMR signals of guest-A@(**1a**·**2a**) and guest-B@(**1a**·**2a**) appeared independently on the NMR time scale. Thus, comparison of the signal integrations between guest-A@(**1a**·**2a**) and guest-B@(**1a**·**2a**) can be used to evaluate the guest-binding ability of **1a**·**2a** (for example, Fig. 5). Guest molecules **3**–**31** investigated here and the relative guest-binding ability of **1a**·**2a** determined by the competitive encapsulation experiments in $CDCl_3$ are summarized in Chart 1 and Table 1, respectively. Table 1 also contains molecular lengths of guests including van der Waals radii,[20] $\Delta\delta$ values of the terminal methyl protons of *p*-functional groups of the encapsulated guests, and orientational isomeric selectivities of the unsymmetrical guests encapsulated in **1a**·**2a**. The following features (items 1–5) are noteworthy concerning the guest encapsulation in **1a**·**2a**.

Item 1: size selectivity. The molecular lengths of the encapsulated guests are in the range 12.14–15.15 Å. The heterodimeric capsule **1a**·**2a** strictly discriminates a one-carbon atom difference in guests, as well as functional groups. The binding ability of **4** to **1a**·**2a** is 735 times greater than **23**, and **24** was not encapsulated in **1a**·**2a**. The binding ability of **13** to **1a**·**2a** is 27 times greater than **19**, and **26** and **27** were not encapsulated. In contrast to **11** and **21** encapsulated in **1a**·**2a**, **25** and **29**–**31** were not encapsulated, respectively. Thus, a fit between guest and cavity of capsule in size is essential for the encapsulation.[3g,11b,21]

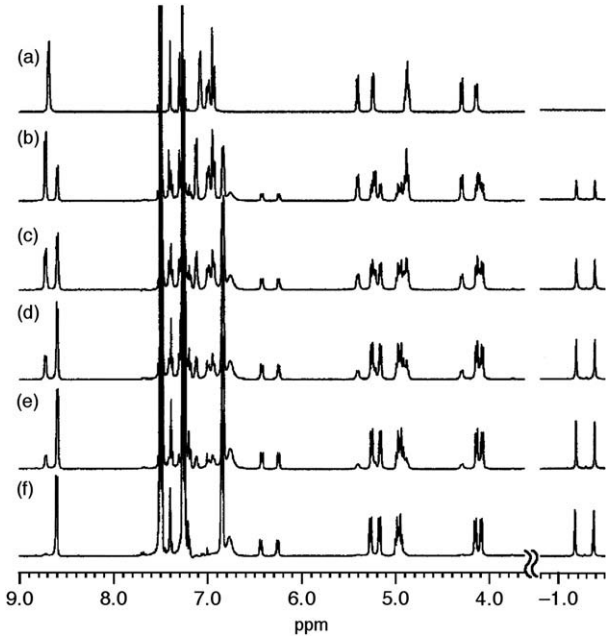


Figure 3. Association behavior of heterodimeric capsule **1a**·**2a** with 4,4′-dimethylbiphenyl **21** monitored by ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): (a) [**1a**·**2a**]=5 mM, (b) [**1a**·**2a**]=[**21**]=5 mM, (c) [**1a**·**2a**]=5 mM and [**21**]=10 mM, (d) [**1a**·**2a**]=5 mM and [**21**]=15 mM, (e) [**1a**·**2a**]=5 mM and [**21**]=25 mM, and (f) [**1a**·**2a**]=5 mM and [**21**]=75 mM.

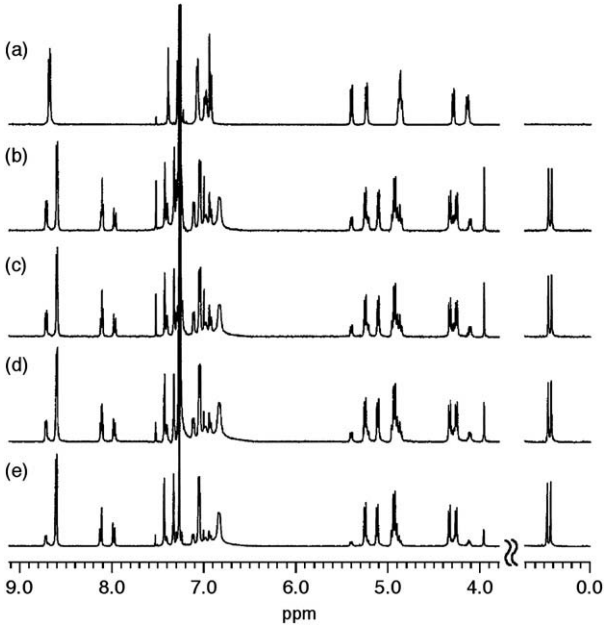


Figure 4. Dilution experiment for the association of **1a**·**2a** with dimethyl terephthalate **11** monitored by ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): (a) [**1a**·**2a**]=5 mM, (b) [**1a**·**2a**]=[**11**]=0.5 mM, (c) [**1a**·**2a**]=[**11**]=0.75 mM, (d) [**1a**·**2a**]=[**11**]=1 mM, and (e) [**1a**·**2a**]=[**11**]=2 mM.

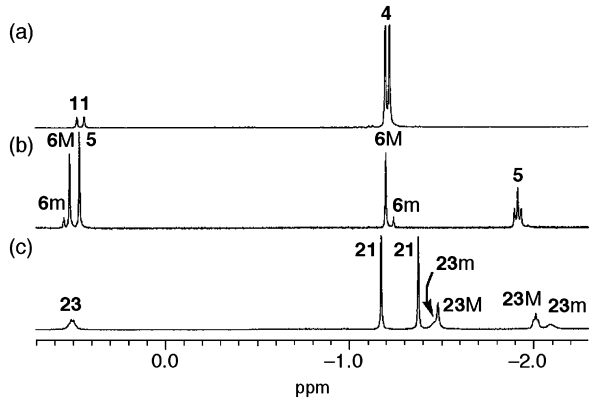


Figure 5. Competitive encapsulation experiments of two kinds of guests in **1a**·**2a** monitored by ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): (a) [**1a**·**2a**]=5 mM and [**4**]=[**11**]=10 mM, (b) [**1a**·**2a**]=5 mM and [**5**]=[**6**]=10 mM, and (c) [**1a**·**2a**]=5 mM and [**21**]=[**23**]=50 mM. 'M' and 'm' show the major and minor orientational isomers, respectively, encapsulated in **1a**·**2a**.

Item 2: CH–π interaction. In a series of *p*-disubstituted-benzene guests with oxygen-containing functional groups and a similar molecular length, the guest-binding ability of **1a**·**2a** increased in the order: **18**<**5** and **11**<**6**<**4**. Furthermore, in marked contrast to **14** encapsulated in **1a**·**2a**, the carbon analogue **28** was not encapsulated. These results clearly indicate that CH–π interaction between the polarized C–H bond of acetoxy, methoxycarbonyl, or methoxy group in guest and the electron-rich aromatic cavity of the capsule **1a**·**2a** as a π-base plays an important role in the encapsulation of guest in **1a**·**2a**,[11b,16] although electrostatic potential repulsion between the lone pairs of the carbonyl oxygen atom of functional groups of guests and the aromatic cavity of **1a**·**2a** should also be considered.[13]

Item 3: isotope effect. Compounds **4**-d_6, **11**-d_6, and **14**-d_6 with the trideuterium-labeled methyl groups (Chart 1) were used to investigate the isotope effect on guest encapsulation in **1a**·**2a**. In all cases investigated here, the guest-encapsulation isotope effect of **1a**·**2a** was $K_H/K_D \geq 1$ in $CDCl_3$ at 23 °C, and increased in the order K[**14**@(**1a**·**2a**)]/K[**14**-d_6@(**1a**·**2a**)] (1.01±0.04)<K[**11**@(**1a**·**2a**)]/K[**11**-d_6@(**1a**·**2a**)] (1.08±0.02)<K[**4**@(**1a**·**2a**)]/K[**4**-d_6@(**1a**·**2a**)] (1.11±0.02). This order would be more or less related to that of acidity of the terminal methyl group of guests. This result suggests that the higher polarizability of a C–H bond relative to a C–D bond would result in stronger CH–π interaction between guest and **1a**·**2a**,[22] although a blue shift of the C–H/C–D stretching frequency upon formation of a CH/CD–π interaction that leads to an increased zero point energy splitting,[23] as well as a volume isotope effect,[24] should also be considered.

Item 4: CH–halogen and halogen–π interactions. The binding abilities of iodo-containing guests **12** and **13** to **1a**·**2a** are greater than **14**, **17**, and **18**, although the molecular lengths of the former guests are somewhat shorter than those of the latter guests. This result suggests that CH–halogen and halogen–π interactions are effective for guest encapsulation.[11b,17,18] It is known that the iodo group is polarized δ(+) in the polar region and δ(−) in the equatorial region of the C–I bond.[17,18b] Thus, there would be CH–I interaction between the polarized inner proton of the methylene-bridge rim of a cavitand and the δ(−) equatorial region of the iodo atom in the C–I bond of a guest, and I–π interaction between the δ(+) polar region of the iodo group and the aromatic cavity of a cavitand.

Item 5: orientational isomerism. The heterodimeric capsule **1a**·**2a** expresses orientational isomerism of encapsulated unsymmetrical guests with high orientational isomeric selectivity

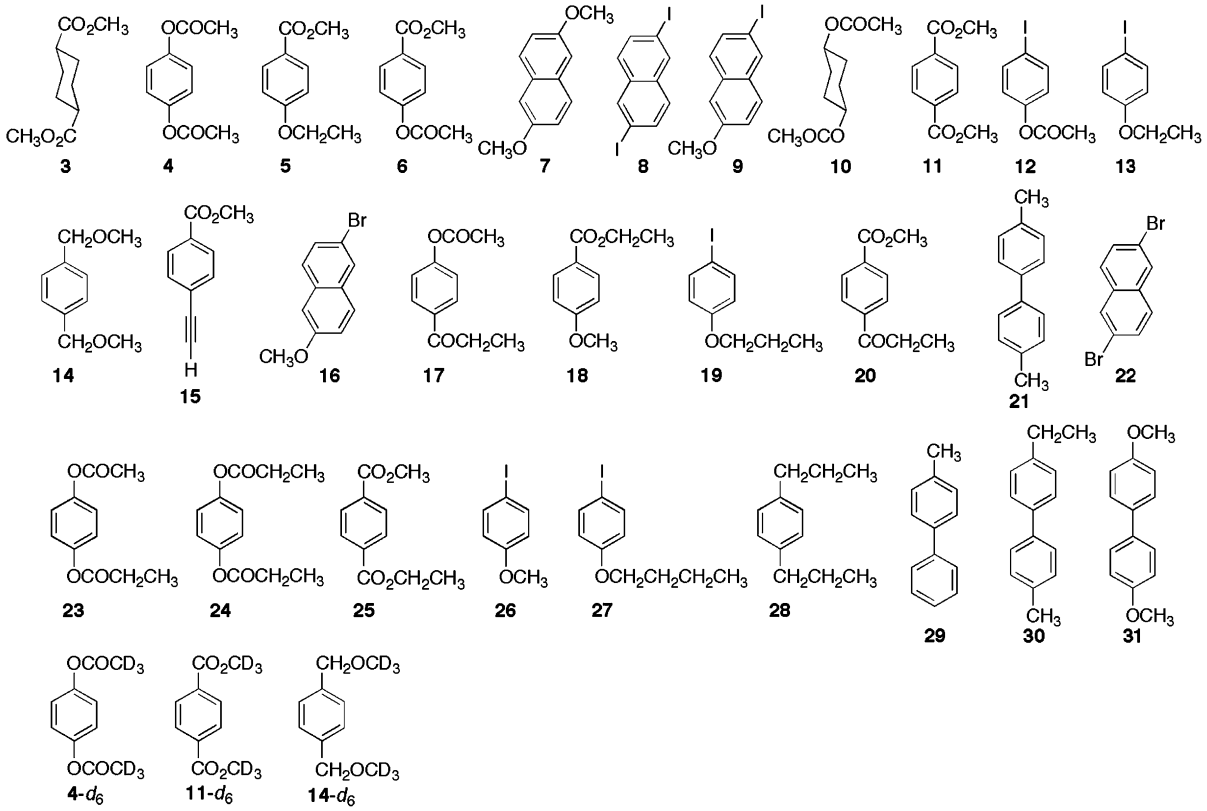


Chart 1. Guest molecules investigated in this study.

Table 1
Relative guest-binding abilities of heterodimeric capsule **1a**·**2a**, molecular lengths of guests, Δδ Values, and orientational isomeric selectivities

Guest no.	Relative binding ability[a]	Molecular length[b] (Å)	$\Delta\delta_{G-CH3}$[c] (ppm)	Orientational isomeric selectivity[d]
3	662	13.83	−3.60, −3.60	—
4	581	13.84	−3.53, −3.50	—
5	199	13.58	−3.43, −3.37	1:0.03
6	164	13.35	−3.54, −3.42	1:0.15
7	160	13.69	−2.86, −2.86	—
8	84	12.81	—	—
9	75	13.24	−3.00	Specific
10	74	13.70	−3.53, −3.54	—
11	73	13.37	−3.52, −3.47	—
12	57	12.14	−3.33	1:0.16
13	52	12.16	−3.11	Specific
14	47	13.18	−3.33, −3.33	—
15	26	12.65	−3.27,[e] −3.12	1:0.49
16	4.1	13.00	nd[f]	Specific
17	3.3	15.14	−3.72, −3.49	1:0.42
18	2.4	13.65	−3.09, −2.79	1:0.33
19	1.9	13.47	−2.87	Specific
20	1.6	13.79	−3.67, −3.56	Specific
21	1.0	13.17	−3.76, −3.56	—
22	0.90	12.34	—	—
23	0.79	15.15	−3.80, −3.30	1:0.38
24	ne[g]	16.46	—	—
25	ne[g]	14.75	—	—
26	ne[g]	10.92	—	—
27	ne[g]	14.50	—	—
28	ne[g]	13.93	—	—
29	ne[g]	12.28	—	—
30	ne[g]	14.45	—	—
31	ne[g]	15.60	—	—

[a] Relative guest-binding ability of **1a**·**2a** determined by the competitive encapsulation experiments in $CDCl_3$ at 23 °C, wherein $K_a=(2.02\pm0.13)\times10^4\ M^{-1}$ for **11**@(**1a**·**2a**) and $K_a=(2.76\pm0.05)\times10^2\ M^{-1}$ for **21**@(**1a**·**2a**).
[b] Molecular lengths of guests including van der Waals radii.[20]
[c] Δδ values ($\delta_{encapsulated\ guest}-\delta_{free\ guest}$) of the terminal methyl protons of *p*-functional groups of the encapsulated guests. For unsymmetrical guests, Δδ values of major orientational isomer are shown here.
[d] Orientational isomeric selectivity of unsymmetrical guest encapsulated in **1a**·**2a**.
[e] Terminal acetylenic proton.
[f] Not determined due to overlapping with other signals.
[g] No encapsulation.

based on the difference in electronic environments of the pyridyl-cavitand **1a** and the phenol-cavitand **2a** (Scheme 1b).[13,25] For the halogen-containing unsymmetrical guests **9**, **12**, **13**, **16**, and **19**, the halogen groups were specifically or preferentially oriented to the cavity of the **1a** unit. For the ester-containing unsymmetrical guests **5**, **6**, **15**, **18**, and **20**, the ester groups were preferentially oriented to the cavity of the **1a** unit. For **17** and **23**, the acetoxy group was preferably oriented to the **1a** unit. The delicate balance among attractive CH–π interaction, CH–halogen (halogen–π) interaction, or electrostatic potential repulsion between the lone pair of the carbonyl oxygen atom of a guest and the aromatic cavity of a cavitand,[13] as well as C═O···HC interaction shown in Figure 1, in a guest–**1a**·**2a** assembly would influence the orientational isomeric selectivity of unsymmetrical guests within **1a**·**2a**.

3. Conclusions

We have described the self-assembly of tetra(4-pyridyl)-cavitand **1** and tetrakis(4-hydroxyphenyl)-cavitand **2** into a heterodimeric capsule **1**·**2** via four PhOH···pyridyl hydrogen bonds in $CDCl_3$, wherein one molecule of 1,4-disubstituted-benzene as a guest is encapsulated to form a ternary complex, guest@(**1**·**2**). The heterodimeric capsule **1**·**2** strictly discriminates a one-carbon atom difference in guests, as well as functional groups. The delicate balance among attractive CH–π interaction, CH–halogen (halogen–π) interaction, C═O···HC interaction, or electrostatic potential repulsion between the lone pair of the carbonyl oxygen atom of a guest and the aromatic cavity of a cavitand in a guest–**1**·**2** assembly would influence the binding ability of guests to **1**·**2**, as well as the orientational isomeric selectivity of unsymmetrical guests within **1**·**2**. Our next projects are (1) theoretical calculations to elucidate the origins of selective or specific orientational isomerism of (unsymmetrical guest)@(**1**·**2**) and (2) study on the rotation behavior of guests within **1**·**2** directed to a supramolecular gyroscope.[26]

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a JEOL JNM-AL400 spectrometer. Synthesis of tetra(4-pyridyl)-cavitand **1a** and tetrakis(4-hydroxyphenyl)-cavitand **2a** with side chains $R=(CH_2)_6CH_3$ were described previously.[9a,13] $CDCl_3$ employed in the ^1H NMR experiments was stored over K_2CO_3 prior to use.

4.2. Synthesis

4.2.1. Tetra(4-pyridyl)-cavitand with side chain $R=CH_2CH(CH_3)_2$ ***1b***

Compound **1b** was synthesized in 85% yield as off-white crystals according to the literature methods.[9a] Mp 382 °C (decomp.); ^1H NMR ($CDCl_3$, 23 °C) δ 8.60 (d, *J*=5.4 Hz, 8H), 7.36 (s, 4H), 6.99 (d, *J*=5.4 Hz, 8H), 5.31 (d, *J*=6.8 Hz, 4H), 5.00 (t, *J*=7.8 Hz, 4H), 4.24 (d, *J*=6.8 Hz, 4H), 2.25 (dd, *J*=7.3 and 7.8 Hz, 8H), 1.71–1.61 (m, 4H), 1.09 (d, *J*=6.4 Hz, 24H); ^{13}C NMR ($CDCl_3$, 23 °C) δ 152.2, 149.5, 142.0, 138.6, 126.8, 124.9, 121.2, 100.5, 39.1, 34.7, 26.1, 22.9. Anal. Calcd for $C_{68}H_{68}N_4O_8\cdot H_2O$: C, 75.11; H, 6.49; N, 5.15. Found: C, 74.89; H, 6.51; N, 5.03.

4.2.2. Tetrakis(4-hydroxyphenyl)-cavitand with side chain $R=CH_2CH(CH_3)_2$ ***2b***

Compound **2b** was synthesized in 70% yield as off-white crystals according to the literature methods.[13] Mp 291 °C (decomp.); ^1H NMR (DMSO-d_6, 23 °C) δ 9.40 (s, 4H), 7.70 (s, 4H), 6.84 (d, *J*=8.8 Hz, 8H), 6.68 (d, *J*=8.8 Hz, 8H), 5.18 (d, *J*=7.3 Hz, 4H), 4.81 (t, *J*=7.8 Hz, 4H), 4.24 (d, *J*=7.3 Hz, 4H), 2.32 (dd, *J*=7.3 and 7.8 Hz, 8H), 1.58–1.48 (m, 4H), 1.00 (d, *J*=6.4 Hz, 24H); ^{13}C NMR (DMSO-d_6, 23 °C) δ 156.2, 152.0, 138.1, 131.1, 128.9, 123.5, 121.1, 114.6, 99.6, 38.5, 34.9, 26.0, 22.7. Anal. Calcd for $C_{72}H_{72}O_{12}\cdot H_2O$: C, 75.37; H, 6.50. Found: C, 75.18; H, 6.39.

4.2.3. Heterodimeric capsule ***1a·2a***[13]

Tetra(4-pyridyl)-cavitand **1a** (61.88 mg) and tetrakis(4-hydroxyphenyl)-cavitand **2a** (64.88 mg) were placed in a 5 mL volumetric flask, to which was added $CDCl_3$. The resulting slightly heterogeneous mixture was sonicated at room temperature for a few minutes to give a clear solution of **1a**·**2a** (10 mM), which was used as a stock solution of **1a**·**2a** for ^1H NMR study. ^1H NMR ($CDCl_3$, 23 °C) δ 10.63 (br s, 4H), 8.72 (d, *J*=5.9 Hz, 8H), 7.41 (s, 4H), 7.30 (s, 4H), 7.12 (d, *J*=5.9 Hz, 8H), 6.99 (d, *J*=8.4 Hz, 8H), 6.93 (d, *J*=8.4 Hz, 8H), 5.40 (d, *J*=6.9 Hz, 4H), 5.22 (d, *J*=6.8 Hz, 4H), 4.88 (t, *J*=7.9 Hz, 8H), 4.30 (d, *J*=6.9 Hz, 4H), 4.11 (d, *J*=6.8 Hz, 4H), 2.28–2.45 (m, 16H), 1.22–1.62 (m, 80H), 0.93 (t, *J*=6.7 Hz, 24H).

4.3. X-ray data collection and crystal structure determination of (methyl 4-ethoxybenzoate)@(1b·2b)

The data were measured using a Bruker APEX II CCD area detector, using Mo Kα graphite monochromated radiation (λ=0.71073 Å). The structure was solved by direct methods using the program SHELXS-97.[27] The refinement and all further calculations were carried out using SHELXL-97.[27] The H-atoms were

included in calculated positions and treated as riding atoms using the SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-square on F^2. Crystal data and structure refinement are listed in Table S1, and ORTEP view is shown in Figure S1 in Supplementary data. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 699622. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture, and Technology, Japan (No. 17350067).

Supplementary data

Crystal data, structure refinement, and ORTEP view of (methyl 4-ethoxybenzoate)@(**1b**·**2b**) are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.093.

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15. The dimensions of inner cavity including van der Waals radii were defined as the distance between both cavity ends, and the average distance between opposite (across) inner protons of the methylene-bridge rim (O–CH_{in}H$_{out}$–O) of the respective **1b** and **2b** units. The dimensions of equatorial portal including van der Waals radii were defined as the average distance between the outer proton of the methylene-bridge rim (O–CH$_{in}H_{out}$–O) of the **1b** unit and that of the **2b** unit, and the mean distance of average distance between basal carbon atoms on two neighboring *p*-pyridyl groups of the **1b** unit and average distance between those on two neighboring *p*-phenol groups of the **2b** unit.
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19. The ^{1}H NMR chemical shifts of guest-free **1a**·**2a** did not change upon dilution of a solution of **1a**·**2a** in $CDCl_3$ at 23 °C to at least 0.5 mM. Thus, **1a**·**2a** is formed even in the absence of a guest and thermodynamically stable at least at concentrations greater than 0.5 mM in $CDCl_3$. On the other hand, the ^{1}H NMR spectrum of a 2:1 mixture of **1a** and **2a** in $CDCl_3$ gave averaged signals for the **1a** unit, indicating that exchange between guest-free **1a**·**2a** and free **1a** is fast on the NMR time scale. In contrast, upon addition of 1 equiv of **11** to this mixture, **11**@(**1a**·**2a**) and free **1a** were independently observed in a 1:1 mole ratio. This result indicates that exchange between **11**@(**1a**·**2a**) and free **1a** is slow on the NMR time scale. Thus, **1a**·**2a** is stabilized upon guest encapsulation.
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