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Orientational Isomerism Controlled by the Difference in Electronic Environments of a Self-Assembling Heterodimeric Capsule

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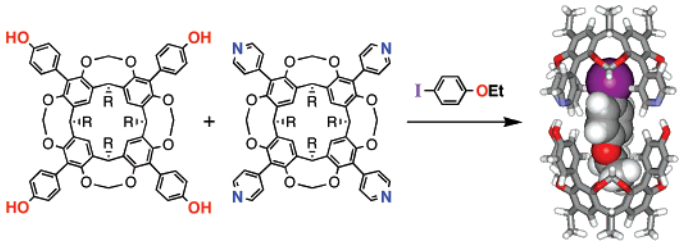
Received December 14, 2006



Tetrakis(4-hydroxyphenyl)-cavitand **1** and tetra(4-pyridyl)-cavitand **2** self-assemble into a heterodimeric capsule **1·2** via four ArOH···pyridyl hydrogen bonds in $CDCl_3$. The **1·2** expresses the orientational isomerism of an encapsulated unsymmetrical guest with high orientational selectivity because the electronic environment of the **1** unit is different from that of the **2** unit. For *p*-ethoxyiodobenzene and 2-iodo-6-methoxynaphthalene encapsulated in **1·2**, the iodo group is specifically oriented to the cavity of the **2** unit. The orientational isomeric selectivity for methyl *p*-acetoxybenzoate and methyl *p*-ethoxybenzoate within **1·2** is 1:0.11 and 1:<0.05, respectively, wherein the methyl ester group is preferentially oriented to the cavity of the **2** unit. The delicate balance among electrostatic potential repulsion, CH−π interaction, or CH−halogen (halogen−π) interaction, in **1·2**−guest assembly influences the orientational isomeric selectivity of unsymmetrical guests within **1·2**.

Introduction

One of the outstanding challenges in the field of nanoscience is the creation and use of self-assembling nanospaces such as molecular capsules. Stereoisomerism upon guest(s) encapsulation in self-assembling capsules offers a new concept in physical organic chemistry as well as supramolecular chemistry.[1] Heterodimeric capsules (i.e., assembly of south and north hemispheres) provide an unsymmetrical nanospace.[2,3] Orientational isomerism emerges from the encapsulation of an unsymmetrical guest in a heterodimeric capsule (Scheme 1a),[4] which may endow a heterodimeric capsule with potential as a building block for molecular devices.[1,5] Recently, we have reported the guest-templated assembly of a bowl-shaped tetracarboxyl-cavitand and a tetra(3-pyridyl)-cavitand into a heterodimeric capsule.[6] In that system, however, the origin of orientational isomerism was unclear because the south hemisphere was different from the north hemisphere in both the structural and the electronic

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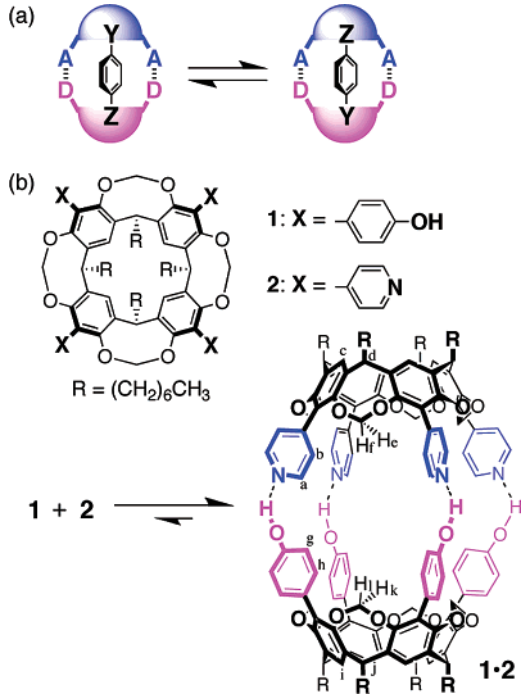
(1) Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 2068−2078 and references therein.

(2) For self-assembling heterodimeric capsules of calix[4]arenes or calix[4]resorcinarene-cavitands via hydrogen bonds or ionic interactions, see: (a) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255−8258. (b) Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282−4288. (c) Castellano, R. K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3657−3663. (d) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264−1267. (e) Higler, I.; Grave, L.; Breuning, E.; Verboom, W.; de Jong, F.; Fyles, T. M.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2000**, 1727−1734. (f) Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 7876−7882. (g) Corbellini, F.; Fiammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569−6575. (h) Corbellini, F.; Knegtel, R. M. A.; Grootenhuis, P. D. J.; Crego-Calame, M.; Reinhoudt, D. N. *Chem.*—Eur. J. **2005**, *11*, 298−307. (i) Koblenz, T. S.; Dekker, H. L.; d. Koster, C. G.; v. Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun.* **2006**, 1700−1702.

10.1021/jo062563k CCC: $37.00
Published on Web 03/31/2007

SCHEME 1. (a) Orientational Isomerism of an Unsymmetrical Guest within a Heterodimeric Capsule and (b) Self-assembly of 1 and 2 into a Heterodimeric Capsule 1·2



environments. To understand the nature of orientational isomerism and to explain the orientational isomeric selectivities, it is desirable to simplify a heterodimeric capsule in which south and north hemispheres have similar structural environments, but significantly different electronic environments. Here, we report the self-assembly of tetrakis(4-hydroxyphenyl)-cavitand **1** and tetra(4-pyridyl)-cavitand **2**[3a] into a heterodimeric capsule **1·2** in a rim-to-rim fashion via four ArOH···pyridyl hydrogen bonds (Scheme 1b). We present how the orientational isomerism of unsymmetrical guests with high orientational selectivity emerges within the self-assembling unsymmetrical nanospace **1·2**.

Results and Discussion

Formation of Heterodimeric Capsule and Guest Encapsulation. Tetrakis(4-hydroxyphenyl)-cavitand **1** was synthesized by the Suzuki cross-coupling reaction of tetraiodo-cavitand[7] with 4-(hydroxyphenyl)boronic acid pinacol ester. The phenol-

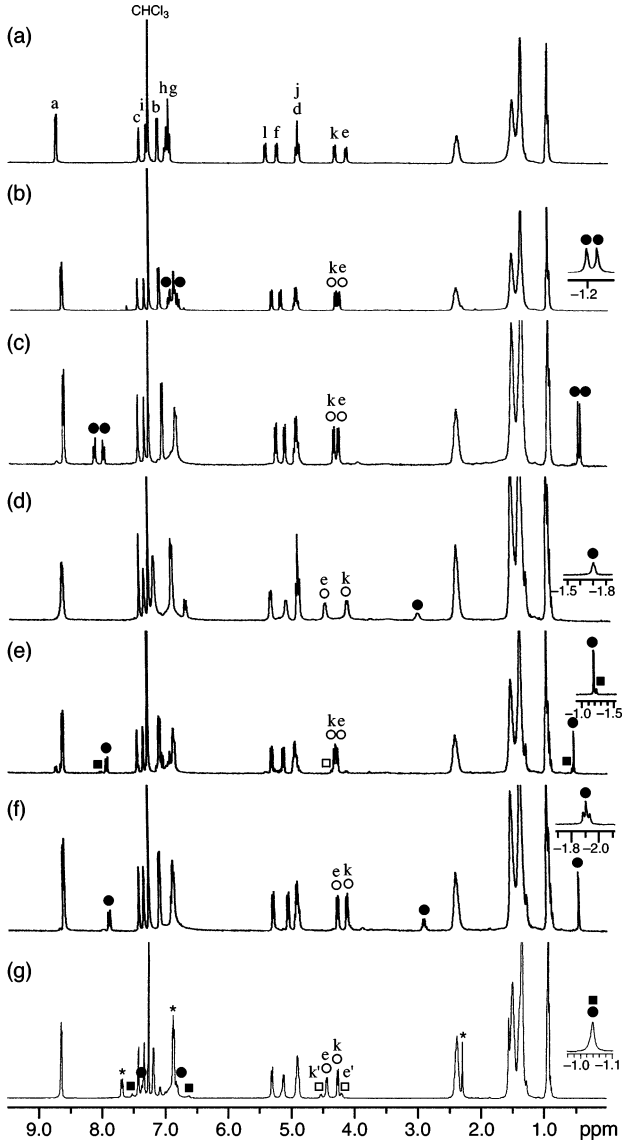


FIGURE 1. Association behavior of heterodimeric capsule **1·2** with guests monitored by ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): (a) [**1·2**] = 5 mM, (b) [**1·2**] = [*p*-diacetoxybenzene] = 5 mM, (c) [**1·2**] = [dimethyl terephthalate] = 5 mM, (d) [**1·2**] = [*p*-ethoxyiodobenzene] = 5 mM, (e) [**1·2**] = [methyl *p*-acetoxybenzoate] = 5 mM, (f) [**1·2**] = [methyl *p*-ethoxybenzoate] = 5 mM, and (g) [**1·2**] = 5 mM and [*p*-acetoxyiodobenzene] = 10 mM. The signals marked a−l are assigned in Scheme 1b. The representative signals of encapsulated guest and guest-encapsulating **1·2** are marked with solid and open circles, respectively, and those of a minor orientational isomer are marked with solid and open squares, respectively. The signals of a free guest are marked with an asterisk.

cavitand **1** by itself is scarcely soluble in $CDCl_3$, whereas it becomes soluble upon addition of 1 equiv of the pyridyl-cavitand **2**. The ^{1}H NMR spectrum of a 1:1 mixture of **1** and **2** in $CDCl_3$ (5 mM each) showed a single highly symmetrical species (C_{4v} symmetry) as shown in Figure 1a, indicating the formation of heterodimeric capsule **1·2** (Scheme 1b). The *p*-pyridyl α- and *β*-protons of **1·2** were shifted downfield by 0.11 and 0.14 ppm, respectively, relative to those of free **2**, because of hydrogen bonding with the *p*-phenol OH group of the **1** unit which appeared at 10.63 ppm. The 2D NOESY spectrum also supported the formation of **1·2**, wherein the NOE correlation was observed between the α-proton of **1** and the α-proton of **2**

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(4) For orientational isomerism of a guest or two different guests encapsulated in a covalently bound heterodimeric capsule, see: (a) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2345−2348. (b) Ihm, C.; Jo, E.; Kim, J.; Paek, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2056−2059.

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TABLE 1. Diffusion Coefficients of Pyridyl-Cavitand 2, Heterodimeric Capsule 1·2, and *p*-Diacetoxybenzene@(1·2) in $CDCl_3$ at 30 °C Measured by Diffusion NMR (600 MHz)[a]

entry	sample	signals	diffusion coefficient[b] (10^{-10} m^2 s^{-1})
1	**2**[c]	**2**	4.82 ± 0.12
2	**1·2**[d]	**1·2**	3.74 ± 0.09
3	*p*-diacetoxybenzene@(**1·2**)[e]	**1·2**	3.84 ± 0.13
		p-diacetoxybenzene in **1·2**	3.85 ± 0.09
4	*p*-diacetoxybenzene@(**1·2**) + *p*-diacetoxybenzene[f]	**1·2**	4.17 ± 0.11
		p-diacetoxybenzene in **1·2**	4.28 ± 0.08
		free *p*-diacetoxybenzene	13.4 ± 0.3

[a] Diffusion time = 100 ms. Grad 1 = 1 ms for entries 1 and 4, and 1.5 ms for entries 2 and 3. Grad 1 amp = 100 mT/m to 0.297 T/m, 16 points. Relaxation delay = 10 s. [b] Value is average of diffusion coefficients of all signals. [c] [**2**] = 5 mM. [d] [**1**] = [**2**] = 5 mM. [e] [**1**] = [**2**] = [*p*-diacetoxybenzene] = 5 mM. [f] [**1**] = [**2**] = 5 mM and [*p*-diacetoxybenzene] = 10 mM (see, Figure S3).

(Figure S1). The chemical shifts of **1·2** did not change upon dilution of a solution of **1·2** in $CDCl_3$ to at least 0.5 mM.

The ^{1}H NMR spectrum of a 1:1 mixture of **1·2** and *p*-diacetoxybenzene in $CDCl_3$ (5 mM each) showed quantitative formation of guest-encapsulating **1·2**, namely, *p*-diacetoxybenzene@(**1·2**) (Figure 1b). The ^{1}H NMR spectrum of a 1:2 mixture of **1·2** and *p*-diacetoxybenzene showed *p*-diacetoxybenzene@(**1·2**) and free *p*-diacetoxybenzene in a 1:1 mole ratio as independent signals (Figure S2). This result indicates that one molecule of *p*-diacetoxybenzene is encapsulated in **1·2** and that exchange between *p*-diacetoxybenzene@(**1·2**) and free *p*-diacetoxybenzene is slow on the NMR time scale. Diffusion-ordered NMR experiments afforded further evidence for **1·2** (diffusion coefficient (D) = 3.74 ± 0.09 × 10^{-10} m^2 s^{-1}) and *p*-diacetoxybenzene@(**1·2**) (D = 3.84 ± 0.13 × 10^{-10} m^2 s^{-1} for **1·2** signals and D = 3.85 ± 0.09 × 10^{-10} m^2 s^{-1} for guest signals), as shown in Table 1 and Figure S3. The cold-spray ionization mass spectrometry also supported the **1·2**-*p*-diacetoxybenzene assembly in $CHCl_3$ (Figure S4). It is noted that four ArOH···pyridyl hydrogen bonds can result in **1·2** of high thermodynamic stability. In the ^{1}H NMR experiments of [**1**] = [**2**] = [*p*-diacetoxybenzene] = 5 mM, the guest encapsulation was maintained 70% and 40% even in 10% and 20% DMSO-d_6−$CDCl_3$, respectively, and was completely decomposed in 40% DMSO-d_6−$CDCl_3$ (Figure S5).

As the electronic environment of **1** is different from that of **2**, the *p*-diacetoxybenzene within **1·2** was desymmetrized, and its ^{1}H NMR signals in $CDCl_3$ appeared as two singlet peaks for the acetoxy protons with $\Delta\delta$ values ($\delta_{\text{encapsulated guest}} - \delta_{\text{free guest}}$) of −3.52 and −3.50 ppm and as two doublet peaks for the aromatic protons with $\Delta\delta$ of −0.30 and −0.15 ppm (Figures 1b and 2a). The $\Delta\delta$ values indicate that the acetoxy groups are oriented to both aromatic cavity ends of **1·2** and the guest does not tumble within **1·2** on the NMR time scale. The 2D NOESY spectrum of *p*-diacetoxybenzene@(**1·2**) showed the NOE correlations between the guest acetoxy proton of −1.22 ppm ($\Delta\delta$ = −3.52) and the inner proton of the methylene-bridge rim (O−$CH_{in}H_{out}$−O) of the **2** unit and between the acetoxy proton of −1.20 ppm ($\Delta\delta$ = −3.50) and that of the **1** unit (Figure S6). The (dimethyl terephthalate)@(**1·2**) shown in Figures 1c and 2b also exhibited the similar NOE correlations (Figure S7). These results clearly indicate that the protons of the desymmetrized guest shifted relatively more upfield are oriented toward the **2** unit, and those shifted relatively less upfield are oriented toward the **1** unit. This finding is an important clue to determining the orientation of major and minor orientational isomers in (unsymmetrical guest)@(**1·2**).

Orientational Isomerism of Unsymmetrical Guest within Heterodimeric Capsule. The heterodimeric capsule **1·2** expresses orientational isomerism of encapsulated unsymmetrical guests with high orientational selectivity based on *the difference in electronic environments of the **1** and **2** units*. The orientational isomeric selectivity of (unsymmetrical guest)@(**1·2**) with $\Delta\delta$ values is summarized in Figure 2c−h. In some cases, the orientation of major and minor orientational isomers was assigned by NOE experiments (Figure S7). Furthermore, the assignment for the orientation of iodo-containing unsymmetrical guests within **1·2** was based on the fact that the ^{1}H NMR signal of the inner proton of the methylene-bridge rim (O−$CH_{in}H_{out}$−O) of the cavitand unit in contact with the iodo group of a guest is shifted more downfield than that of the other cavitand unit because of CH−halogen interaction.[6,8] The assignment for the orientation of unsymmetrical guests with oxygen-containing functional groups was based on the aforementioned finding that the ^{1}H NMR signal of a guest moiety oriented toward the **2** unit is shifted more upfield than that oriented toward the **1** unit. The ratio of major and minor orientational isomers was determined by the ^{1}H NMR integration ratio of independent signals for *p*-substituents of a guest or inner protons of the methylene-bridge rims of **1·2**.

For *p*-ethoxyiodobenzene@(**1·2**) and 2-iodo-6-methoxynaphthalene@(**1·2**), the iodo group was specifically oriented to the cavity of the **2** unit (Figures 1d, S10, and 2c,d). *The cavitand **1** with electron-donating p-phenol group is more electron-rich than the cavitand **2** with electron-withdrawing p-pyridyl group*. It is known that the iodo group is polarized $\delta(+)$ in the polar region and $\delta(-)$ in the equatorial region of the C−I bond.[9] In this respect, CH−I interaction between the polarized inner proton of the methylene-bridge rim of a cavitand and the $\delta(-)$ equatorial region of the iodo atom in the C−I bond of a guest[6,8] would be more favorable in the **2** unit than in the **1** unit (Figure 3a). For I−π interaction,[6,10] both the $\delta(-)$ equatorial and $\delta(+)$ polar regions of the iodo group have contact with the aromatic cavity of a cavitand.

The orientational isomeric selectivity for (methyl *p*-acetoxybenzoate)@(**1·2**), (methyl *p*-ethoxybenzoate)@(**1·2**), and (methyl *p*-propanoylbenzoate)@(**1·2**) was 1:0.11, 1:<0.05, and 1:0, respectively (Figures 1e,f and S13). In these cases, the methyl ester group was preferentially or specifically oriented to the cavity of the **2** unit (Figure 2e−g). For these unsymmetrical guests, CH−π interaction between a guest with polarized C−H bond and the aromatic cavity of a cavitand as a π-base is an important factor,[6,11] and it would be more favorable in the **1**

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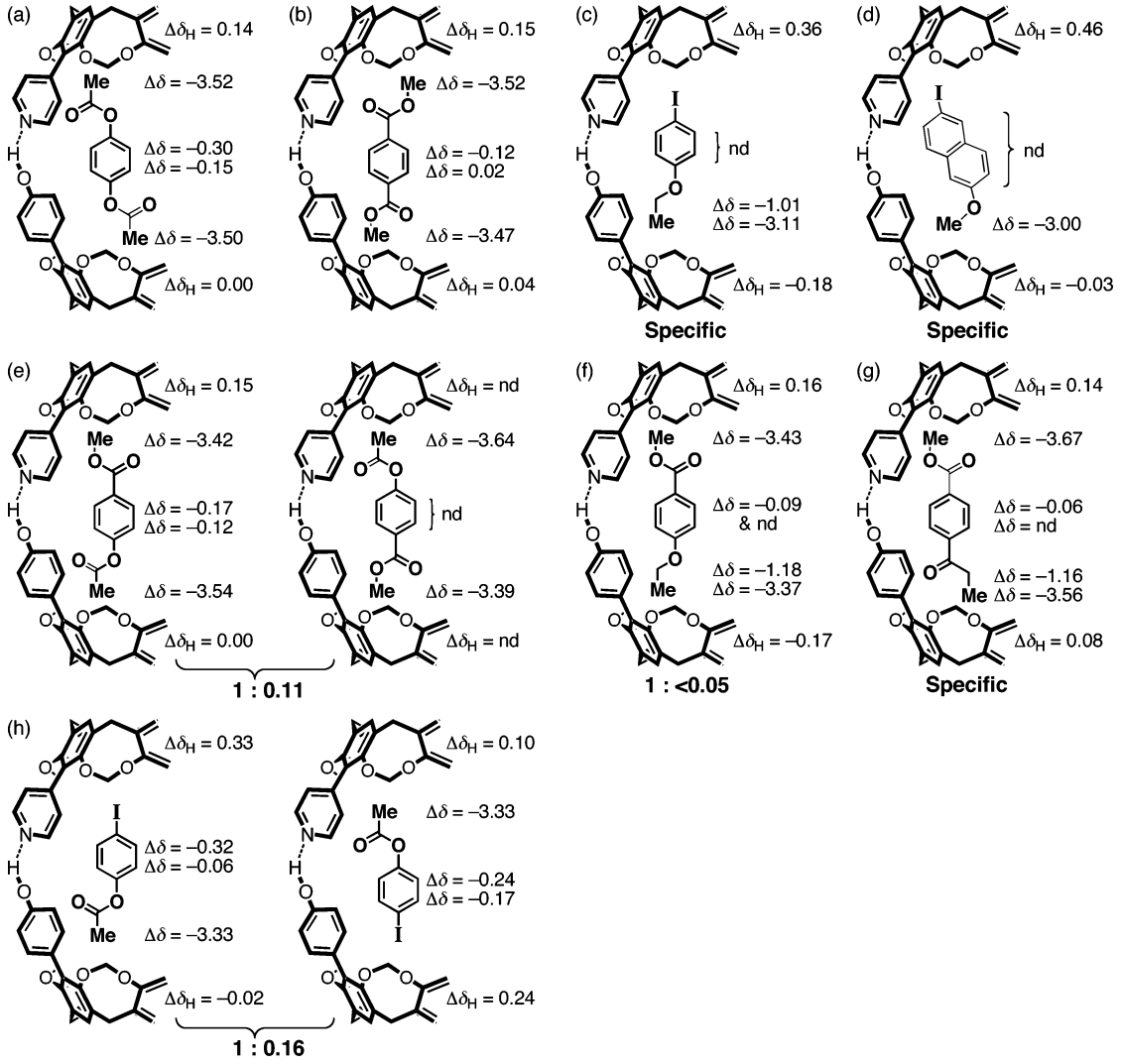

FIGURE 2. Schematic representation of the orientational isomer and selectivity of (unsymmetrical guest)@(**1·2**), the chemical shift changes of the encapsulated guest relative to the free guest ($\Delta\delta$, ppm), and the chemical shift changes of the inner protons of methylene-bridge rims of guest@(**1·2**) relative to those of guest-free **1·2** ($\Delta\delta_H$, ppm), monitored by ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): (a) *p*-diacetoxybenzene@(**1·2**), (b) (dimethyl terephthalate)@(**1·2**), (c) *p*-ethoxyiodobenzene@(**1·2**), (d) 2-iodo-6-methoxynaphthalene@(**1·2**), (e) (methyl *p*-acetoxybenzoate)@(**1·2**), (f) (methyl *p*-ethoxybenzoate)@(**1·2**), (g) (methyl *p*-propanoylbenzoate)@(**1·2**), and (h) *p*-acetoxyiodobenzene@(**1·2**).

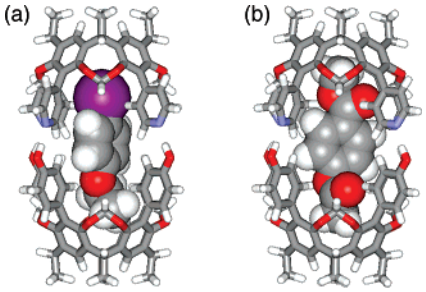

FIGURE 3. Molecular models of (a) *p*-ethoxyiodobenzene@(**1·2**) and (b) (methyl *p*-acetoxybenzoate)@(**1·2**), calculated with PM3 level of HyperChem.

unit than in the **2** unit. However, the orientation of methyl *p*-ethoxybenzoate within **1·2** cannot be explained only by CH−π interaction. The direction of the carbonyl oxygen atom of a guest should also be noteworthy.[12] In (methyl *p*-acetoxybenzene)@(**1·2**), the carbonyl oxygen atom of the methyl ester group is directed inwardly to the cavity end of **1·2**, whereas the carbonyl oxygen atom of the acetoxy group is directed outwardly to the cavity end of **1·2** (Figures 2e and 3b). The carbonyl oxygen atom of the methyl ester group has contact with the aromatic cavity of a cavitand. Therefore, electrostatic potential repulsion between the lone pair of the carbonyl oxygen atom of the methyl ester group and the aromatic cavity of a cavitand would be somewhat larger than that between the acetoxy group and cavitand. Thus, the methyl ester group was preferentially oriented to the relatively electron-poor cavity of the **2** unit rather than the relatively electron-rich cavity of the **1** unit so as to minimize the electrostatic potential repulsion. On the basis of the orientational isomeric selectivity (Figure 2e−g), the electrostatic potential repulsion between oxygen-containing functional groups of guests and **1·2** would increase in the order of $-OCH_2CH_3 \approx -C(O)CH_2CH_3 < -OC(O)CH_3 < -C(O)OCH_3$. The orientational isomeric selectivity of *p*-acetoxyiodoben-

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zene@(**1·2**) was 1:0.16, wherein the iodo and acetoxy groups were preferentially oriented to the **2** and **1** units, respectively, so as to maximize CH−I and CH−π interactions and to minimize electrostatic potential repulsion (Figures 1g and 2h vs Figure 2c).

Conclusion

We have shown the self-assembly of tetrakis(4-hydroxyphenyl)-cavitand **1** and tetra(4-pyridyl)-cavitand **2** into a heterodimeric capsule **1·2** via four ArOH···pyridyl hydrogen bonds with high thermodynamic stability. The self-assembling **1·2** expresses orientational isomerism of encapsulated unsymmetrical guests with high orientational selectivity based on the difference in electronic environments of the **1** and **2** units. The delicate balance among electrostatic potential repulsion between the lone pair of the carbonyl oxygen atom of a guest and the aromatic cavity of a cavitand, attractive CH−π interaction, or attractive CH−halogen (halogen−π) interaction in a **1·2**−guest assembly influences the orientational isomeric selectivity of unsymmetrical guests within **1·2**. Studies exploring how appropriate guests can be encapsulated in the heterodimeric capsule **1·2**, with functions directed toward molecular switches and supramolecular gyroscopes, are in progress.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300, 400, or 600 MHz. ^{13}C NMR spectra were recorded at 75.3 MHz. Tetra(4-pyridyl)-cavitand **2** (R = $(CH_2)_6CH_3$)[3a] and tetraiodo-cavitand (R = $(CH_2)_6CH_3$)[7] were synthesized according to the literature. $CDCl_3$ and DMSO-d_6 were dried over anhydrous K_2CO_3 and molecular sieves 4A, respectively, prior to use. Commercially available reagents were used without any purification.

Tetrakis(4-hydroxyphenyl)-cavitand (1). To a mixture of tetraiodo-cavitand (2.50 g, 1.74 mmol), $PdCl_2(PPh_3)_2$ (0.305 g, 0.435 mmol, 0.25 equiv), $AsPh_3$ (1.07 g, 3.49 mmol, 2.0 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (3.83 g, 17.4 mmol, 10 equiv), and Cs_2CO_3 (8.50 g, 26.1 mmol, 15 equiv) under an argon atmosphere were added 1,4-dioxane (230 mL) and H_2O (9 mL). The resulting mixture was stirred at 110 °C for 21 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was acidified to pH 4 with 1 M HCl at 0 °C. After evaporation of solvents, the residue was taken up in EtOAc and then filtered. The filtrate was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After evaporation of solvents, the residue was subjected to column chromatography on silica gel eluted with EtOAc−$CHCl_3$ (1:2 and then 2:1), and then purified by recrystallization from Et_2O−hexane to give **1** (1.87 g, 83% yield) as off-white crystals. Mp 268−269 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 23 °C) δ 0.85 (t, J = 6.7 Hz, 12H), 1.20−1.52 (m, 40H), 2.35−2.52 (m, 8H), 4.23 (d, J = 7.4 Hz, 4H), 4.64 (t, J = 8.0 Hz, 4H), 5.16 (d, J = 7.4 Hz, 4H), 6.68 (d, J = 8.5 Hz, 8H), 6.83 (d, J = 8.5 Hz, 8H), 7.69 (s, 4H), 9.38 (s, 4H). ^{13}C NMR (75.3 MHz, DMSO-d_6, 23 °C) δ 13.9, 22.0, 27.7, 28.9, 29.1, 29.7, 31.1, 37.1, 99.7, 114.7, 120.9, 123.6, 128.9, 131.1, 138.0, 152.0, 156.2. Anal. Calcd for $C_{84}H_{96}O_{12}\cdot H_2O$: C, 76.68; H, 7.51. Found: C, 76.54; H, 7.38.

Heterodimeric Capsule (1·2). Tetrakis(4-hydroxyphenyl)-cavitand **1** (64.88 mg) and tetra(4-pyridyl)-cavitand **2** (61.88 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 **1·2** (10 mM), which was used as a stock solution of **1·2** for ^{1}H NMR study. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C) δ 0.93 (t, J = 6.7 Hz, 24H), 1.22−1.62 (m, 80H), 2.28−2.45 (m, 16H), 4.11 (d, J = 6.8 Hz, 4H), 4.30 (d, J = 6.9 Hz, 4H), 4.88 (t, J = 7.9 Hz, 8H), 5.22 (d, J = 6.8 Hz, 4H), 5.40 (d, J = 6.9 Hz, 4H), 6.93 (d, J = 8.4 Hz, 8H), 6.99 (d, J = 8.4 Hz, 8H), 7.12 (d, J = 5.9 Hz, 8H), 7.30 (s, 4H), 7.41 (s, 4H), 8.72 (d, J = 5.9 Hz, 8H), 10.63 (brs, 4H); Negative-mode CSI-MS ($CHCl_3$ as a solvent and Ph_4PCl as a charge carrier; ion source temperature = −20 °C) m/z 2569.0 [**1·2** + Cl]$^-$ (calcd 2570.4).

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

Supporting Information Available: 2D NOESY, DOSY, and CSI-MS spectra of *p*-diacetoxybenzene@(**1·2**), and ^{1}H NMR spectra and NOE data of guest@(**1·2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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