Orientational Isomerism and Binding Ability of Nonsymmetrical Guests Encapsulated in a Self-Assembling Heterodimeric Capsule

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Abstract: The ability of a guest to induce the assembly of tetracarboxyl-cavitand **1** and tetra(3-pyridyl)-cavitand **2** into a heterodimeric capsule **1**·**2**, and the orientational isomerism of nonsymmetrical *p*-disubstituted-benzene guests encapsulated in **1**·**2**, are described. For example, the ability of a guest to induce the assembly of guest⊂(**1**·**2**) increases in the order *p*-iodoaniline ≤ *p*-chloroanisole < *p*-bromoanisole < *N*-methyl-*p*-iodoaniline < *p*-iodoanisole. For these five guests encapsulated in **1**·**2**, the halogen atoms are specifically oriented with respect to the cavity of the **2** unit. By contrast, the orientational isomeric selectivities of *p*-chloroiodobenzene, *p*-bromoiodobenzene, and *p*-methylanisole encapsulated in **1**·**2** are quite low, in the range of 1:1.7 to 1:1. The *ortho*-fluoro derivatives of these three guests, however, are encapsulated in **1**·**2** with a highly selective orientation, in which the substituent next to the fluorine atom greatly prefers the cavity of the **2** unit to that of the **1** unit.

Keywords: cavitands · heterodimeric capsules · orientational isomerism · self-assembly · supramolecular chemistry

Introduction

The stereoisomerism of a guest-encapsulating capsule is noticable when the shape and dimensions of a capsule prevent the guest(s) from exchanging positions or from tumbling on the NMR time scale. In pioneering work, Reinhoudt and co-workers discovered orientational isomerism, in which a single molecule, such as *N*,*N*-dimethylacetamide or 1-methyl-2-pyrrolidinone, adopts two different orientations in the cavity of a covalently bound, heterodimeric capsule composed of a calix[4]arene and a calix[4]resorcinarene-cavitand.[1] Recent supramolecular approaches, based on noncovalent interactions through thermodynamic equilibration, have been viable methods for the formation of various types of molecular capsules.[2,3] Rebek and co-workers reported social isomerism[4] and constellational isomerism[5] by using a hydrogen-bonding-driven, self-assembling cylindrical capsule.[3c] In this system, the coencapsulation of two different guests in the homodimeric capsule induces social isomerism, due to the two different orientations of one nonsymmetrical guest being affected by the presence and nature of the other guest.[4] Constellational isomerism arises from different arrangements involving three molecules of two different small guests coencapsulated in the homodimeric capsule.[5] Stereoisomerism of guest-encapsulating capsules offers a new concept in physical organic chemistry, and should provide a novel type of molecular switch with potential applications in the fields of nanoscale data storage devices and molecular electronics.[1,4,5] Thus, control of the molecular orientation in a capsule is a very important consideration for the development of molecular devices in materials science. However, no studies on orientational isomerism and its control based on a noncovalently self-assembling heterodimeric capsule have been reported.[6]

Recently, we reported the guest-induced assembly of the bowl-shaped tetracarboxyl-cavitand **1** and tetra(3-pyridyl)-cavitand **2** into a heterodimeric capsule **1**·**2** in a rim-to-rim fashion mediated by four $CO_2H\cdots N$ hydrogen bonds. Preliminary results showed that the orientation of a nonsymmetrical *p*-disubstituted-benzene guest encapsulated in **1**·**2** can be controlled (Scheme 1).[7] Here, we comprehensively investigated twenty kinds of nonsymmetrical *p*-disubstituted-benzene guests and report the ability of guests to induce the assembly of guest⊂(**1**·**2**) and their orientational isomerism. We also describe the *ortho*-fluorine-atom effect of guests on orientational isomerism.

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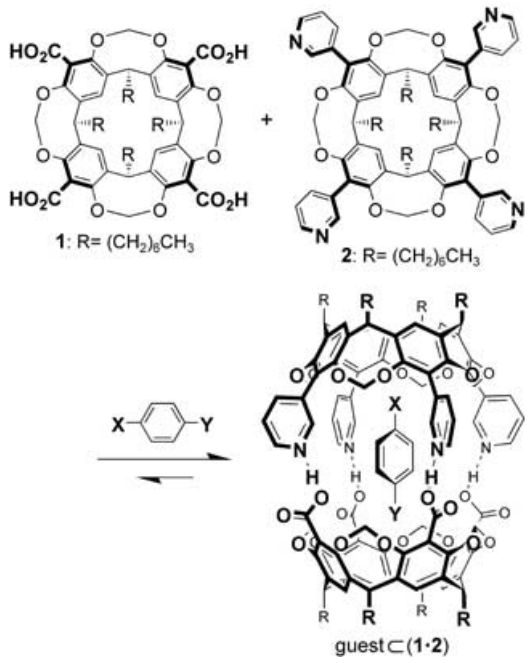
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

 DOI: 10.1002/chem.200500140



Scheme 1. Guest-templated self-assembly of tetracarboxyl-cavitand **1** and tetra(3-pyridyl)-cavitand **2** into a guest-encapsulating heterodimeric capsule guest⊂(**1·2**).

Background:[7] The assembly of guest⊂(**1·2**) was confirmed by conducting ^{1}H NMR spectroscopy and cold-spray ionization mass spectrometry. Upon addition of an appropriate *p*-disubstituted-benzene as a guest, the thermodynamic equilibrium mixture of various aggregates derived from **1** and **2** in $CDCl_3$ is shifted most favorably toward the assembly of the heterodimeric capsule **1·2**, due to guest-templated stabilization through noncovalent interactions. In this circumstance, a guest⊂(**1·2**) becomes the most favored aggregate (Scheme 1).[8] One molecule of *p*-disubstituted-benzene as a guest is encapsulated in **1·2**. The exchange of guests into and out of **1·2** is slow on the NMR time scale. The signals of the encapsulated guest are shifted upfield relative to those of the free guest, attributable to the ring-current effect of the aromatic cavity of **1·2**. As the structural and electronic environments of the **1** unit as the south hemisphere are different from those of the **2** unit as the north hemisphere, inherently symmetrical guests, such as *p*-diiodobenzene and *p*-dimethoxybenzene, lose symmetry by encapsulation in **1·2**. *p*-Disubstituted-benzene encapsulated in **1·2** is arranged with the long axis of the guest along the long axis of **1·2**, and does not tumble within **1·2** on the NMR time scale. Our preliminary work found that the orientation of a nonsymmetrical *p*-disubstituted-benzene encapsulated in **1·2** can be controlled. For example, in the case of *p*-iodoanisole⊂(**1·2**), the iodo and methoxy groups are specifically oriented with respect to the cavities of the **2** and **1** units, respectively. The assignment for the orientation of a nonsymmetrical *p*-disubstituted-benzene encapsulated in **1·2** was based on the following observations from the ^{1}H NMR spectroscopic study: Firstly, the larger upfield-shifted aromatic proton of the encapsulated guest is oriented toward the **2** unit, due to the ring-current effect of the pyridyl group of the **2** unit, and the smaller upfield-shifted aromatic proton is oriented toward the **1** unit. Secondly, the inner protons of the methylene-bridge rims (O-$CH_{in}H_{out}$-O) of *p*-dihalobenzene⊂(**1·2**) are shifted downfield relative to those of *p*-dimethoxybenzene⊂(**1·2**) because of a CH–halogen interaction.[9] It is known that I, Br, and Cl atoms are polarized $\delta(+)$ in the polar region and $\delta(-)$ in the equatorial region of the C–X bond (X = Cl, Br, or I).[10] The specific orientation of *p*-iodoanisole⊂(**1·2**) was also confirmed by conducting X-ray crystallographic analysis.

Results and Discussion

Encapsulation of a nonsymmetrical *p*-disubstituted-benzene guest in 1·2 and orientational isomerism: All ^{1}H NMR spectroscopic (300 MHz) analyses were conducted by using solutions of tetracarboxyl-cavitand **1** and tetra(3-pyridyl)-cavitand **2** (4 mM each) and guest (8 or 120 mM) in $CDCl_3$ at 23 °C. We found that the following nonsymmetrical *p*-disubstituted-benzene guests induce the assembly of **1·2** and are encapsulated in **1·2**: *p*-chloroanisole, *p*-bromoanisole, *p*-ethoxychlorobenzene, *p*-iodoaniline, *N*-methyl-*p*-iodoaniline, *p*-methylanisole, *p*-ethoxytoluene, *p*-iodotoluene, *p*-chloroiodobenzene, and *p*-bromoiodobenzene. The orientational isomeric selectivity or specificity of guest⊂(**1·2**), the chemical shift changes of the encapsulated guest relative to the free guest ($\Delta\delta$), and the chemical shift changes of the inner protons of the methylene-bridge rims of guest⊂(**1·2**) relative to those of *p*-dimethoxybenzene⊂(**1·2**) ($\Delta\delta_H$) are summarized in Figure 1. For comparison, the previously reported data for *p*-iodoanisole, *p*-ethylanisole, *p*-ethyltoluene, and *p*-ethyliodobenzene are also shown in Figure 1.[7] Representative ^{1}H NMR spectra of guest⊂(**1·2**) are shown in Figure 2.[11] The ability of the guest to induce the assembly of guest⊂(**1·2**) is described in the final section.

In the cases of *p*-chloroanisole, *p*-bromoanisole, *p*-iodoanisole, *p*-ethoxychlorobenzene, *p*-iodoaniline, *N*-methyl-*p*-iodoaniline, and *p*-ethyliodobenzene, the halogen atoms were specifically oriented with respect to the cavity of the **2** unit (Figure 1a–f and m). For example, the ^{1}H NMR spectrum of *N*-methyl-*p*-iodoaniline⊂(**1·2**) shows the single species of the aggregate (Figure 1f and Figure 2a). The aromatic *ortho*- and *meta*-protons with respect to the iodo group, and the *N*-methyl proton, are shifted upfield by $\Delta\delta = -0.92$, -0.47, and -3.42 ppm, respectively, relative to those of the free guest. The inner protons of the methylene-bridge rims of the **2** and **1** units in *N*-methyl-*p*-iodoaniline⊂(**1·2**) are shifted downfield by $\Delta\delta_H = 0.35$ ppm and upfield by $\Delta\delta_H = -0.09$ ppm, respectively, relative to those of 1,4-dimethoxybenzene⊂(**1·2**). A CH–halogen interaction between the inner proton of the polarized methylene-bridge of one cavitand unit and the halogen group of a guest,[9] and a CH–π interaction between the polarized methoxy or *N*-methyl group of a guest and the electron-rich aromatic cavity of the other cavitand unit,[12] play important roles in the assembly of guest⊂(**1·2**), as well

as in the specific orientation of an encapsulated nonsymmetrical guest. Space-filling models of the **1** and **2** units and the heterodimeric capsule **1**·**2** are shown in Figure 3.

In the case of *p*-ethylanisole⊂(**1**·**2**), the methoxy group was specifically oriented with respect to the cavity of the **2** unit (Figure 1g).[7] In the case of *p*-ethoxytoluene⊂(**1**·**2**), the methyl group was specifically oriented with respect to the cavity of the **2** unit (Figure 1k). Previously, we could not assign the direction of the specific orientation of *p*-ethyltoluene⊂(**1**·**2**) because of identical chemical shifts of the two aromatic protons of free *p*-ethyltoluene.[7] Now we can deduce that the methyl ($\Delta\delta = -3.41$ ppm) and ethyl ($\Delta\delta_{CH_3CH_2} = -2.48$ ppm) groups are specifically oriented with respect to the cavities of the **2** and **1** units, respectively (Figure 1l), in which the $\Delta\delta$ of the methyl group directed to the **2** unit would be greater than that directed to the **1** unit (vide infra). Thus, for nonhalogenated *p*-disubstituted-benzene guests, the **2** unit of **1**·**2** may prefer a more compact functional group of guest rather than a less compact functional group, due to the narrower and deeper cavity of the **2** unit and the wider and shallower cavity of the **1** unit (Figure 3).

However, the ^{1}H NMR spectrum of *p*-methylanisole⊂(**1**·**2**) showed two sets of species with a 1:1 integration ratio, as revealed by the signals of the methyl and methoxy groups of the encapsulated guest and of the methylene-bridge rims of the capsule (Figure 1h and Figure 2b). This result indicates that the methoxy group of *p*-methylanisole encapsulated in **1**·**2** is oriented with respect to the cavities of the **2** and **1** units in a 1:1 ratio. In marked contrast to *p*-ethylanisole⊂(**1**·**2**) with specific orientation (Figure 1g), the loss of orientational selectivity of *p*-methylanisole⊂(**1**·**2**) would be caused by reduction of the molecular size and volume of *p*-methylanisole relative to *p*-ethylanisole (vide infra). In contrast to *p*-ethyliodobenzene⊂(**1**·**2**) with specific orientation (Figure 1m), the iodo group of *p*-iodotoluene⊂(**1**·**2**) was oriented with respect to the cavities of the **2** and **1** units in a 10.9:1 ratio (Figure 1n and Figure 2e). In the cases of *p*-methylanisole⊂(**1**·**2**) and *p*-iodotoluene⊂(**1**·**2**), the $\Delta\delta$ of the methyl and methoxy groups directed to the cavity of the **2** unit were greater than the $\Delta\delta$ of those directed to the cavity of the **1** unit. The orientational selectivity for *p*-chloroiodobenzene⊂(**1**·**2**) (Figure 1p and Figure 2g) and *p*-bromoiodobenzene⊂(**1**·**2**) (Figure 1r and Figure 2i) was very low, although the iodo group slightly prefers the **2** unit to the **1** unit.

Thus, a nonsymmetrical *p*-disubstituted-benzene-guest⊂(**1**·**2**) decreases the orientational selectivity when 1) both substituents are of similar character, 2) one of the two substituents is not effective for CH–halogen or CH–π interaction, and/or 3) the guest volume per cavity volume of **1**·**2** is relatively small (vide infra).

The *ortho*-fluorine-atom effect on orientational isomerism: We identified an *ortho*-fluorine-atom effect in the control of the orientation of a nonsymmetrical *p*-disubstituted-benzene guest that is inherently encapsulated in **1**·**2** with low or no orientational selectivity. When one fluorine atom is introduced to the aromatic ring of such a nonsymmetrical *p*-disubstituted-benzene, the substituent next to the fluorine atom greatly prefers the **2** unit to the **1** unit.

As mentioned above, *p*-methylanisole⊂(**1**·**2**) has no orientational selectivity. In marked contrast, the methoxy group of 2-fluoro-4-methylanisole⊂(**1**·**2**) preferred the **2** unit to the **1** unit in a 2.63:1 ratio (Figure 1h vs i and Figure 2b vs c), whereas the methyl group of 3-fluoro-4-methylanisole⊂(**1**·**2**) preferred the **2** unit to the **1** unit in a 5.26:1 ratio (Figure 1j and Figure 2d).[13] In the ^{1}H NMR spectrum of 3-fluoro-4-methylanisole⊂(**1**·**2**), the $\Delta\delta$ of the methyl and methoxy groups of the guest in the major isomer were −2.80 and −3.10 ppm, respectively, and those in the minor isomer were −2.17 and −3.41 ppm, respectively. The orientational selectivity of I:Me oriented to the **2** unit changed from 10.9:1 in *p*-iodotoluene⊂(**1**·**2**) to 1.06:1 in 2-fluoro-4-iodotoluene⊂(**1**·**2**), indicating that the methyl group next to the fluorine atom greatly prefers the **2** unit to the **1** unit (Figure 1n vs o and Figure 2e vs f). In *p*-dihalobenzene guests with very low orientational selectivity, orientational isomerism was dramatically changed by the introduction of a fluorine atom into the aromatic ring. Although the orientational selectivity of *p*-chloroiodobenzene⊂(**1**·**2**) was I:Cl = 1.69:1 for the **2** unit (Figure 1p and Figure 2g), the iodo and fluoro atoms of 1-chloro-3-fluoro-4-iodobenzene⊂(**1**·**2**) were specifically oriented with respect to the cavity of the **2** unit (Figure 1q and Figure 2h). In the ^{1}H NMR spectrum, the inner protons of the methylene-bridge rims of the **1** and **2** units in *p*-chloroiodobenzene⊂(**1**·**2**) appeared as four doublet peaks with $\Delta\delta_H = -0.05$ and 0.32 ppm, respectively, for the major isomer and $\Delta\delta_H = 0.27$ and −0.02 ppm, respectively, for the minor isomer. In contrast, those in 1-chloro-3-fluoro-4-iodobenzene⊂(**1**·**2**) appeared as two doublet peaks with $\Delta\delta_H = -0.09$ and 0.32 ppm, respectively, indicating only one isomer. The orientational selectivity for *p*-bromoiodobenzene⊂(**1**·**2**) was I:Br = 1.09:1 for the **2** unit (Figure 1r and Figure 2i), whereas the bromo and fluoro atoms of 1-bromo-2-fluoro-4-iodobenzene⊂(**1**·**2**) were specifically oriented with respect to the cavity of the **2** unit (Figure 1s and Figure 2j). The iodo and fluoro atoms of 1-bromo-3-fluoro-4-iodobenzene⊂(**1**·**2**) were specifically oriented with respect to the cavity of the **2** unit (Figure 1t and Figure 2k). Even at 50 °C in $CDCl_3$, the exchange of these guests into and out of **1**·**2** was slow, and the encapsulated guests did not tumble on the NMR time scale, so that the orientational selectivity remained unchanged.

Thus, by the introduction of a fluorine atom into the aromatic ring of a nonsymmetrical *p*-disubstituted-benzene with inherently low or no orientational selectivity, the substituent next to the fluorine atom greatly prefers the cavity of the **2** unit to the cavity of the **1** unit. A theoretical calculation indicates that the dipole moment of **1**·**2** is 17.55 D with the direction from the **1** unit to the **2** unit.[14] In the case of *p*-iodoanisole⊂(**1**·**2**), the direction of the dipole moment of *p*-iodoanisole (2.95 D) is antiparallel to that of **1**·**2**, although a large total dipole moment still remains. On the other hand, in the cases of the fluorine-containing-guest⊂(**1**·**2**), the di-

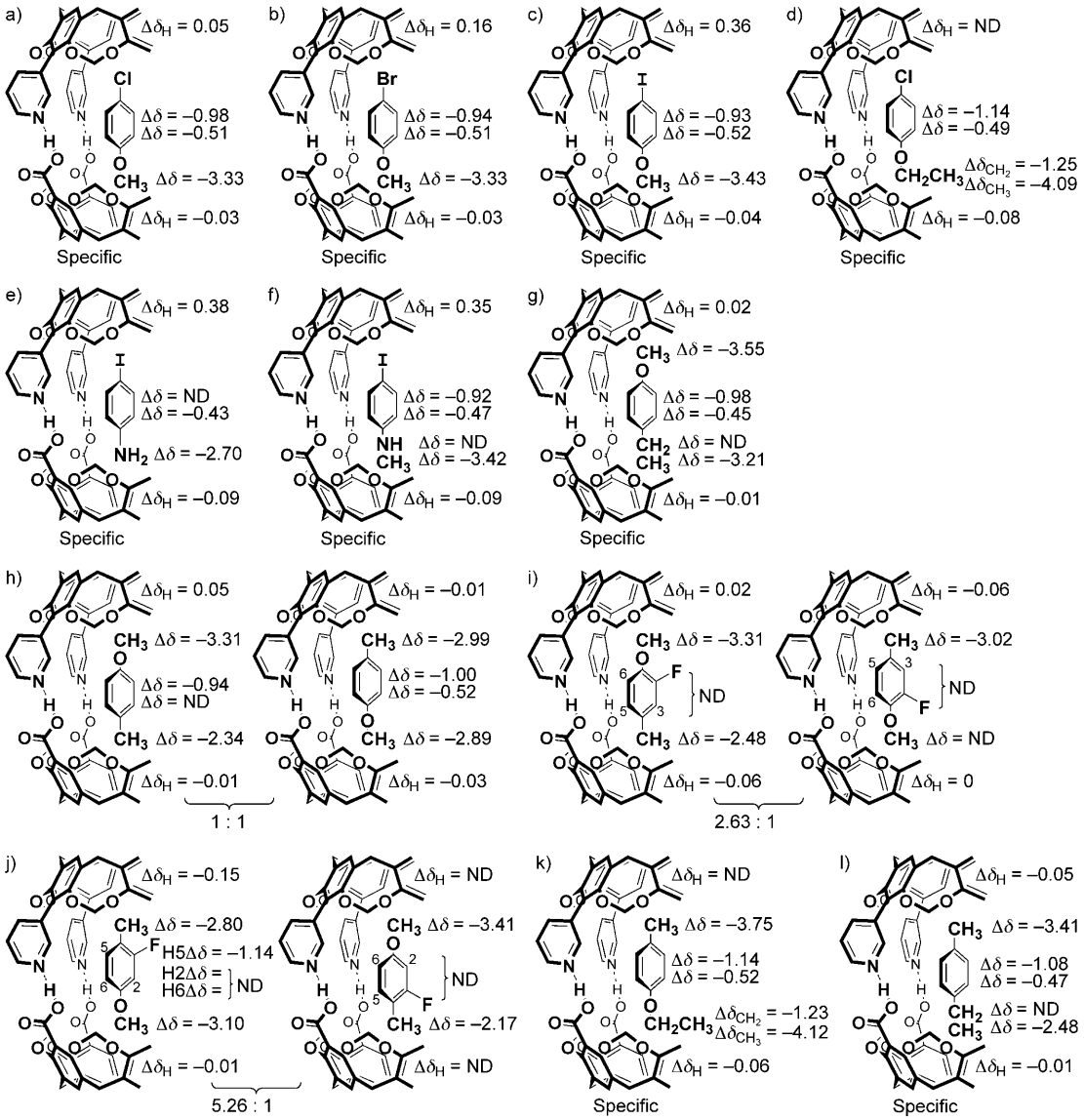


Figure 1. Schematic representation of the orientational isomer and selectivity of guest⊂(**1**·**2**), the chemical shift changes of the encapsulated guest relative to the free guest ($\Delta\delta$, in ppm), and the chemical shift changes of the inner protons of methylene-bridge rims of guest⊂(**1**·**2**) relative to those of *p*-dimethoxybenzene⊂(**1**·**2**) ($\Delta\delta_H$, in ppm), monitored by ^{1}H NMR spectroscopy (300 MHz) in $CDCl_3$ at 23 °C: a) *p*-chloroanisole⊂(**1**·**2**), b) *p*-bromoanisole⊂(**1**·**2**), c) *p*-iodoanisole⊂(**1**·**2**), d) *p*-ethoxychlorobenzene⊂(**1**·**2**), e) *p*-iodoaniline⊂(**1**·**2**), f) *N*-methyl-*p*-iodoaniline⊂(**1**·**2**), g) *p*-ethylanisole⊂(**1**·**2**), h) *p*-methylanisole⊂(**1**·**2**), i) 2-fluoro-4-methylanisole⊂(**1**·**2**), j) 3-fluoro-4-methylanisole⊂(**1**·**2**), k) *p*-ethoxytoluene⊂(**1**·**2**), l) *p*-ethyltoluene⊂(**1**·**2**), m) *p*-ethyliodobenzene⊂(**1**·**2**), n) *p*-iodotoluene⊂(**1**·**2**), o) 2-fluoro-4-iodotoluene⊂(**1**·**2**), p) *p*-chloroiodobenzene⊂(**1**·**2**), q) 1-chloro-3-fluoro-4-iodobenzene⊂(**1**·**2**), r) *p*-bromoiodobenzene⊂(**1**·**2**), s) 1-bromo-2-fluoro-4-iodobenzene⊂(**1**·**2**), and t) 1-bromo-3-fluoro-4-iodobenzene⊂(**1**·**2**). ND = not determined.

rection of the dipole moment of the fluorine-containing guest is pseudoparallel to that of **1**·**2**. Therefore, the dipole moment would not be a crucial factor for the orientational isomerism of the encapsulated guest. At this stage, it remains difficult to experimentally elucidate the reason(s) for specific or selective orientation of nonsymmetrical 1,4-disubstituted-benzene guests encapsulated in **1**·**2**, as well as the *ortho*-fluorine-atom effect. The signal of the C2-proton of the 3-pyridyl group of the fluorine-containing-guest⊂(**1**·**2**) was scarcely shifted compared with that of the corresponding non-fluorine-containing-guest⊂(**1**·**2**).[15] It is conceivable that the introduction of the *ortho*-fluorine atom into a nonsymmetrical 1,4-disubstituted-benzene guest causes electronic repulsion between the fluorine atom and the carboxyl OH oxygen atom of the **1** unit. This may be one of the reasons why the substituent next to the fluorine atom prefers the **2** unit to the **1** unit. Further studies, such as theoretical calculations, are required before these questions can be answered.

Ability of a guest to induce the assembly of guest⊂(1·2) (scope and limitation): In the competition experiments, the

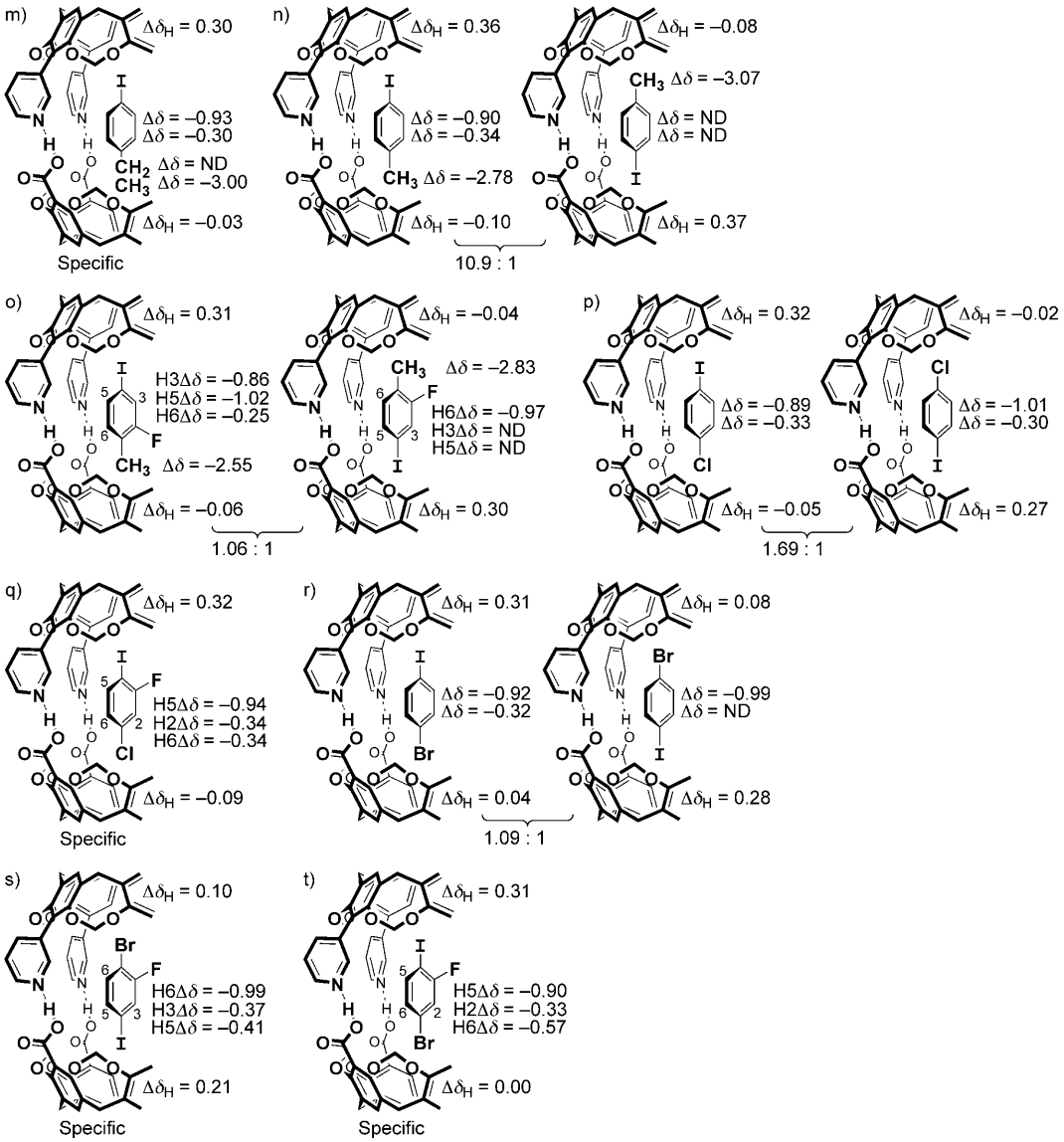


Fig. 1 (cont.)

signals of guest-A⊂(**1**·**2**) and guest-B⊂(**1**·**2**) appeared independently on the NMR time scale, as shown in Figure 4. Thus, comparison of the signal integrations between guest-A⊂(**1**·**2**) and guest-B⊂(**1**·**2**) can be used to evaluate the ability of the guest to induce the assembly of guest⊂(**1**·**2**). The ability of the guest to induce guest⊂(**1**·**2**) relative to *p*-dibromobenzene⊂(**1**·**2**) in $CDCl_3$ is summarized in Figure 5. The values in parentheses indicate the guest volume per the cavity volume of **1**·**2** (hereafter, packing coefficient, PC).[16–18] For comparison, the previously reported data for *p*-diiodobenzene⊂(**1**·**2**) and *p*-dimethoxybenzene⊂(**1**·**2**),[7] and for nonencapsulated guests are also shown in Figure 5. The following six features are noteworthy concerning the assembly of guest⊂(**1**·**2**) in $CDCl_3$.

1) In all cases of guest⊂(**1**·**2**), the PCs are in the range 0.525–0.623, which agrees with the concept of 55% solution proposed by Rebek.[4,19] The ability to induce assembly of *p*-ethyliodobenzene with PC = 0.623 is lower than for *p*-iodotoluene with PC = 0.554, indicating that *p*-ethyliodobenzene is more cramped than *p*-iodotoluene in the cavity of **1**·**2**, although the orientational selectivity of the former is much higher than that of the latter. *p*-Diiodobenzene and *p*-dimethoxybenzene possess the greatest ability to induce the assembly of guest⊂(**1**·**2**) (38-fold and 29-fold relative to *p*-dibromobenzene, respectively), whereas *m*-diiodobenzene and *m*-dimethoxybenzene cannot induce the formation of **1**·**2**. In a series of *p*-iodoaniline derivatives, the ability to induce assembly of *N*-methyl-*p*-iodoaniline with PC = 0.603 is 20-fold greater than *p*-iodoaniline with PC = 0.529, whereas *N*,*N*-dimethyl-*p*-iodoaniline with PC = 0.675 is not encapsulated in **1**·**2**. In a series of *p*-dialkylbenzenes, *p*-ethyltoluene with PC = 0.572 is encapsulated in **1**·**2**, whereas *p*-diethylben-

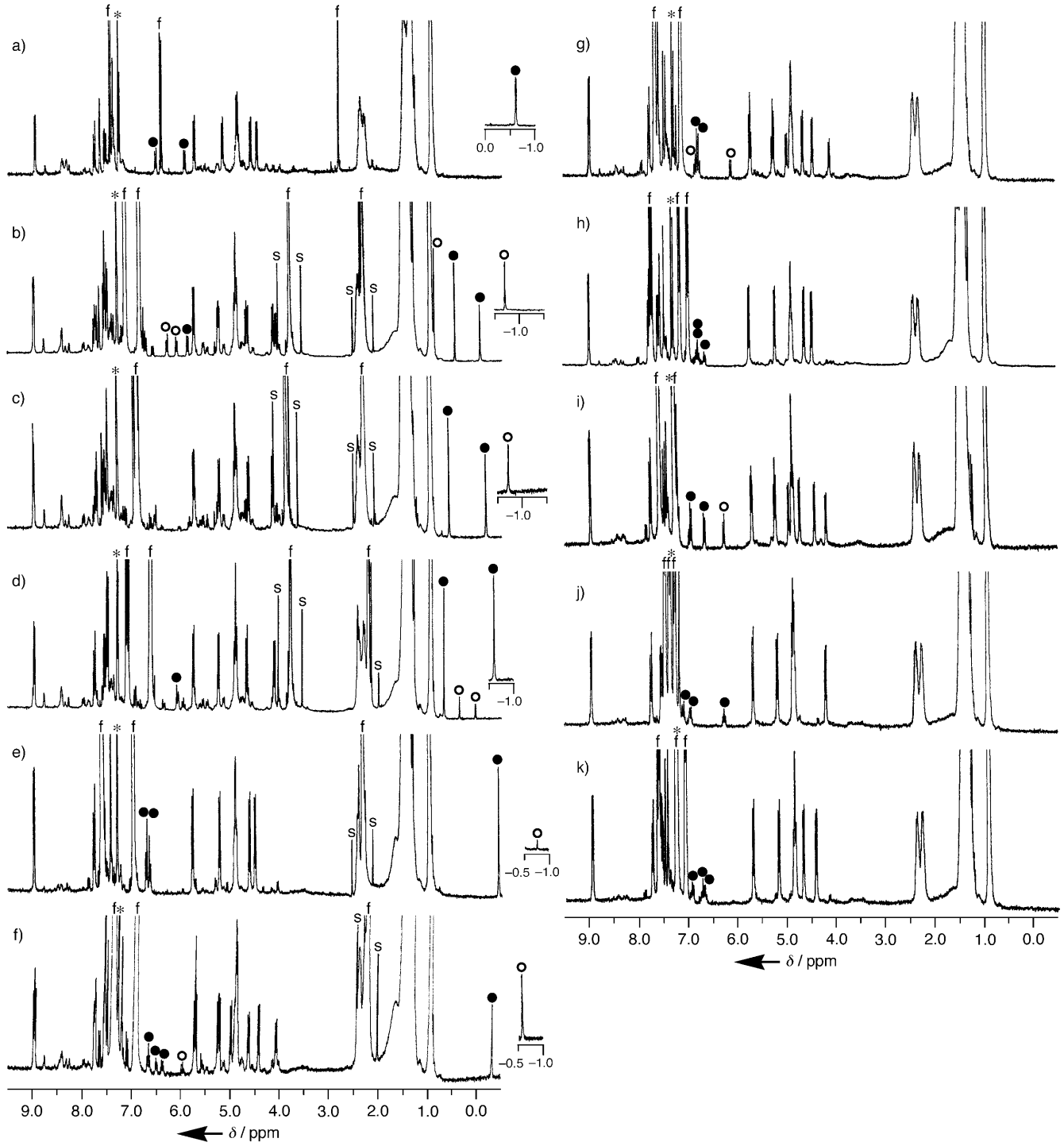


Figure 2. ^{1}H NMR spectra (300 MHz) of a 1:1 mixture of **1** and **2** (4 mM each) in $CDCl_3$ at 23 °C in the presence of a) *N*-methyl-*p*-iodoaniline, b) *p*-methylanisole, c) 2-fluoro-4-methylanisole, d) 3-fluoro-4-methylanisole, e) *p*-iodotoluene, f) 2-fluoro-4-iodotoluene, g) *p*-chloroiodobenzene, h) 1-chloro-3-fluoro-4-iodobenzene, i) *p*-bromoiodobenzene, j) 1-bromo-2-fluoro-4-iodobenzene, and k) 1-bromo-3-fluoro-4-iodobenzene. For *N*-methyl-*p*-iodoaniline and the other guests, 2 and 30 equivalents were used, respectively. The signals of major and minor orientational isomers of the guest encapsulated in **1·2** are marked with a solid circle and open circle, respectively. The signals of free guest, spinning sidebands, and the residual solvent are marked "f", "s", and *, respectively.

zene with PC = 0.644 and *p*-xylene with PC = 0.502 are not encapsulated in **1·2**, although *p*-[D_{10}]-xylene induces the assembly of **1·2** when used as the NMR solvent in place of $CDCl_3$. Thus, the heterodimeric capsule **1·2** is size- and shape-selective, and can discriminate between a methyl group and a methylene group of guest molecules.

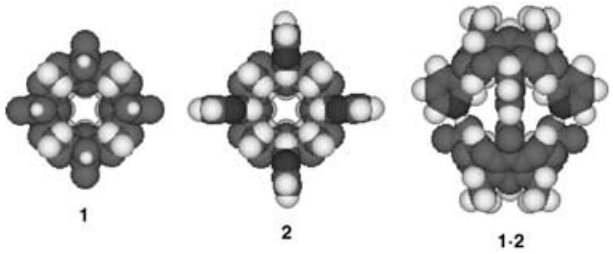


Figure 3. Space-filling models of the **1** and **2** units and the heterodimeric capsule **1·2**.

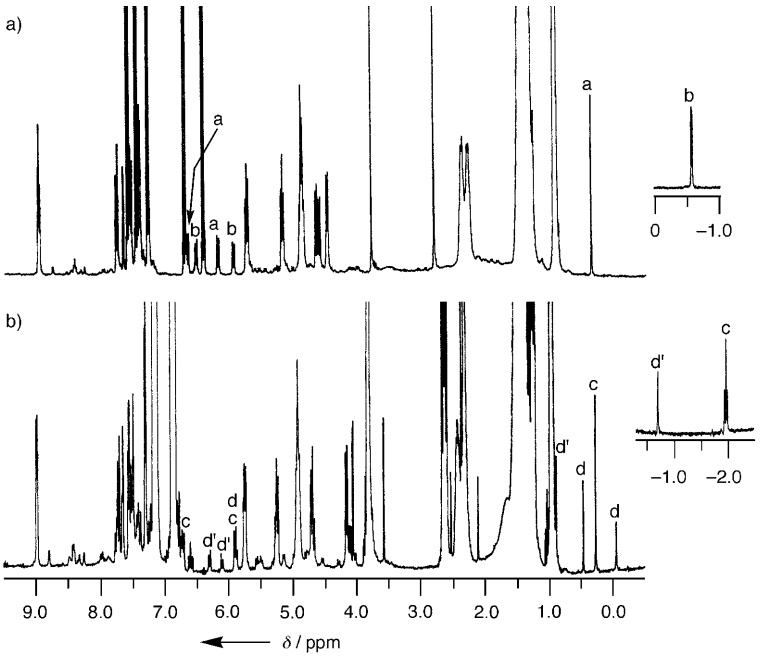


Figure 4. Representative results of the competition experiments. ^{1}H NMR spectra (300 MHz) of a 1:1 mixture of **1** and **2** (4 mM each) in $CDCl_3$ at 23 °C in the presence of a) a 1:1 mixture of *p*-iodoanisole and *N*-methyl-*p*-iodoaniline (8 mM each), in which the encapsulated guests are marked "a" and "b", respectively, and b) a 1:1 mixture of *p*-ethylanisole and *p*-methylanisole (120 mM each), in which the encapsulated guests are marked "c" and "d" ("d′"), respectively.

2) In the cases of *p*-diiodobenzene, *p*-ethylanisole, and *p*-ethoxytoluene with almost the same PC, the ability of the guest to induce the assembly of guest⊂(**1·2**) increases in the order *p*-ethoxytoluene (0.33) < *p*-ethylanisole-(0.74) ≪ *p*-diiodobenzene (38). This result indicates that the capsule–guest CH–halogen interaction between the inner proton of the polarized methylene-bridge of the cavitand unit and the halogen group of a guest,[9] as well as the guest–capsule CH–π interaction between the polarized methoxy of a guest and the electron-rich aromatic cavity of the cavitand unit,[12] plays an important role in the assembly of guest⊂(**1·2**). In the cases of *p*-dimethoxybenzene versus *p*-ethylanisole, and *p*-methylanisole versus *p*-ethyltoluene, with similar molecular shape and length, the ability to induce assembly increases in the order *p*-ethylanisole (0.74) ≪ *p*-dimethoxybenzene (29), and *p*-ethyltoluene (0.11) < *p*-methylanisole (0.85), respectively. This result also shows the importance of the CH–π interaction.
3) In two series of *p*-dihalobenzene⊂(**1·2**) and *p*-haloanisole⊂(**1·2**), the ability to induce assembly increases in the order *p*-dibromobenzene (1) < *p*-chloroiodobenzene (1.2) < *p*-bromoiodobenzene (9.8) < *p*-diiodobenzene (38), and *p*-chloroanisole (0.83) < *p*-bromoanisole (4.9) < *p*-iodoanisole (22), respectively. *p*-Dichlorobenzene and *p*-fluoroiodobenzene are not encapsulated in **1·2**. This result arises from a combination of the degree of CH–halogen interaction (Cl < Br < I)[9a] and the PC.
4) *p*-Cyanoanisole, *N*-methyl-*p*-cyanoaniline, and *N*-methyl-*p*-nitroaniline are not encapsulated in **1·2**, although these PCs are similar to that of *p*-bromoanisole. In these guests, the lone pair(s) of electrons of the cyano and nitro groups would cause electronic repulsion of the electron-rich aromatic cavity of **1·2**. In contrast, as I, Br, and Cl atoms bearing lone pairs of electrons are polarized δ(+) in the polar region and δ(−) in the equatorial region of the C–X bond (X = Cl < Br < I), as shown in Figure 6,[10] the polar region of these halogen atoms can interact with the aromatic cavity of **1·2** through a halogen–π interaction,[20] and the equatorial region of these halogen atoms interacts with the inner proton of the methylene-bridge rim of **1·2** through a CH–halogen interaction.[9]
5) No encapsulation in **1·2** occurs with *p*-(trifluoromethyl)iodobenzene, *p*-(trifluoromethyl)anisole, and *p*-bis(trifluoromethyl)benzene. This result is in marked contrast to *p*-iodotoluene, *p*-methylanisole, and *p*-ethyltoluene. The fluorine atom possesses the highest electronegativity and the smallest van der Waals radius among the halogen atoms. Therefore, the fluorine atom is much less polarized in the polar and equatorial regions of the C–F bond (entirely electronegative) and would cause electronic repulsion of the aromatic cavity of **1·2**. Thus, a guest bearing the *p*-trifluoromethyl group is not encapsulated in **1·2**, in spite of the good shape and size of the guest for the cavity of **1·2**.
6) The ability of *p*-ethoxychlorobenzene with PC = 0.596 to act as a guest is less than that of *p*-ethoxytoluene with PC = 0.604. The chlorine atom of *p*-ethoxychlorobenzene

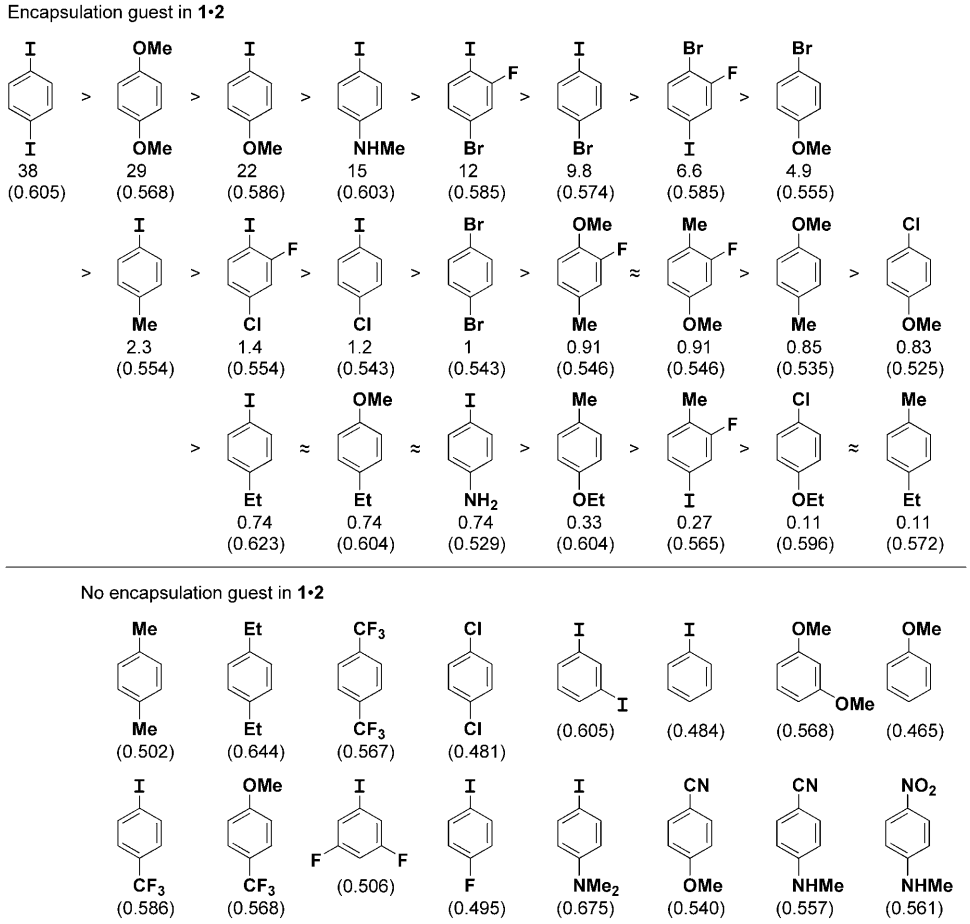


Figure 5. Ability of guests to induce the assembly of guest⊂(**1**·**2**) relative to *p*-dibromobenzene⊂(**1**·**2**), evaluated by performing competition experiments under the conditions of [**1**]=[**2**]=4 mM and [guest-A]=[guest-B]= 8 or 120 mM in $CDCl_3$ at 23 °C. The values in parentheses indicate the guest volume per cavity volume of **1**·**2** (packing coefficient, PC).

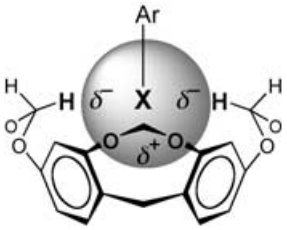


Figure 6. Schematic representation for the polarization of the halogen atom with $\delta(+)$ in the polar region and $\delta(-)$ in the equatorial region of the C–X bond (X = Cl, Br, or I). The polar region can induce halogen–π interaction, and the equatorial region can induce CH–halogen interaction.

may be less polarized in the polar and equatorial regions of the C–Cl bond, such as the C–F bond, due to the resonance effect of the electron-donating *p*-ethoxy group. Thus, the chlorine atom of *p*-ethoxychlorobenzene would be liable to cause electronic repulsion of the aromatic cavity of **1**·**2**. The ability of *p*-chloroanisole with PC = 0.525 to act as a guest is greater than that of *p*-ethoxychlorobenzene, probably due to the PC of the former being smaller, as well as a more effective CH–π interaction of the methoxy group compared with the ethoxy group.

Conclusion

We have described the guest-induced assembly of tetracarboxyl-cavitand **1** and tetra(3-pyridyl)-cavitand **2** into the heterodimeric capsule **1**·**2** in a rim-to-rim fashion mediated by four $CO_2H\cdots N$ hydrogen bonds. The guest-templated stabilization through capsule–guest CH–halogen interaction, guest–capsule CH–π interaction, and/or guest–capsule halogen–π interaction plays an important role in the assembly of guest⊂(**1**·**2**), in addition to the size, shape, and volume of the guest relative to the cavity of **1**·**2**. These interactions are also very important for the control of the orientation of nonsymmetrical *p*-disubstituted-benzene guests. A nonsymmetrical *p*-disubstituted-benzene guest is encapsulated in **1**·**2** with a specific orientation upon satisfaction of the following conditions: 1) both substituents have different characters, such as electronic property or size, 2) one or both of the two substituents are effective in CH–halogen, CH–π, and/or halogen–π interaction(s), and 3) the volume and size of a guest are compatible with those of the cavity of **1**·**2** with packing coefficients in the range of 0.525 to 0.623. Otherwise, a *p*-disubstituted-benzene-guest⊂(**1**·**2**) loses the orientational specificity and decreases the orientational selectivity, or a guest cannot induce the assembly of **1**·**2**. However, when a fluorine atom is introduced to the aromatic ring of a nonsymmetrical *p*-disubstituted-benzene with low or no orientational selectivity, the substituent next to the fluorine atom greatly prefers the **2** unit to the **1** unit (*ortho*-fluorine-atom effect). Our next projects are 1) theoretical calculations to elucidate the origins of selective or specific orientational isomerism and of the *ortho*-fluorine-atom effect, 2) synthesis of a supramolecular gyroscope[21] of fluorine-containing-guest⊂(**1**·**2**) by using an F-probe, and 3) control of the packing alignment of nonsymmetrical-guest⊂(**1**·**2**) in the solid state directed toward nonlinear optical materials.[22]

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz by using a Bruker AC300 spectrometer. Tetracarboxyl-cavitand **1** and tetra(3-pyridyl)-cavitand **2** as host molecules were synthesized according to literature methods.[7] 2-Fluoro-4-methylanisole and 3-fluoro-4-methylanisole as guest molecules were prepared according to literature methods.[13] Other guest molecules were commercially available and used without purification. $CDCl_3$ was dried over anhydrous potassium carbonate prior to use.

^{1}H NMR measurements: All measurements were performed in $CDCl_3$ at 23 °C. A stock solution of a 1:1 mixture of **1** and **2** (8 mM each) in $CDCl_3$ and a stock solution of a guest (16 or 240 mM) in $CDCl_3$ were prepared. The NMR samples were prepared by mixing equal volumes (300 μL) of these two stock solutions in the NMR tubes so that [**1**] = [**2**] = 4 mM and [guest] = 8 or 120 mM, depending on the guest-templating ability. For the competition experiments, a stock solution of a 1:1 mixture of guest-A and guest-B (16 or 240 mM each) in $CDCl_3$ was used to prepare the NMR sample at [**1**] = [**2**] = 4 mM and [guest-A] = [guest-B] = 8 or 120 mM, depending on the guest-templating ability.

Acknowledgements

We thank Professor S. Nagase and Dr. S. Re (Institute for Molecular Science, Japan) for their theoretical calculations of the dipole moments of **1**·**2** and *p*-iodoanisole.

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[16] The molecular modeling of **1**·**2** was carried out by using Macromodel 6.0 (AMBER* force field), and the cavity depth including van der Waals radii was estimated to be 11.3 Å. The internal cavity volume of **1**·**2** was estimated to be 238 Å^3 by the calculation of GRASP (reference [17]). The presence of large holes at the equatorial region of **1**·**2** made the calculation difficult. In the actual calculation, the outer protons of the methylene-bridge rims of **1**·**2** were replaced with propyl groups to reduce the large holes, and a probe of 1.5 Å in diameter was used.

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Received: February 9, 2005
Published online: April 29, 2005