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Structural Properties of Benzimidazole Cavitand and Its Selective Recognition toward 4-Methylbenzamide over 4-Methylanilide

Heung-Jin Choi,* Yeon Sil Park, Jie Song, Seok Ju Youn, Hong-Seok Kim, Sung-Hoon Kim,† Kwangnak Koh,‡ and Kyungsoo Paek§

Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea, Department of Dyeing and Finishing, Kyungpook National University, Daegu 702-701, Korea, College of Pharmacy, Pusan National University, Busan 609-735, Korea, and CAMDRC and Department of Chemistry, Soongsil University, Seoul 156-743, Korea

choihj@knu.ac.kr

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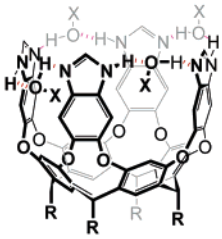
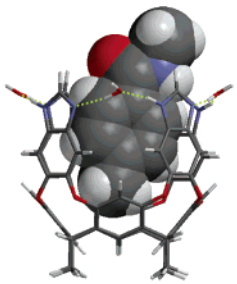


5·4HOX: X = H, Me, CH_3CO or CF_3CO, R = $C_{11}H_{23}$



N,4-dimethylbenzamide@**5**·4H_2O

The conformations and properties of cavitand **5** with four benzimidazole flaps are studied by ^{1}H NMR. The benzimidazole cavitand **5** can form very stable vase structures with an enforced concave cavity by intermolecular hydrogen bonding with four hydroxyl-containing molecules, X-OH, such as methanol (X = Me), acetic acid (X = CH_3CO), and trifluoroacetic acid (X = CF_3CO). The stronger hydrogen bond donor strengths of X-OH are, the stronger hydrogen bonds are formed between the NH and N atoms of the neighboring benzimidazole fragments and the more vase structures of **5**·4HOX are stable. The annular tautomerism of **5** in $CDCl_3/CD_3OD$ (9:1, v/v) due to the proton exchange between NH and N atoms of the neighboring benzimidazole fragments is observed by 400 MHz ^{1}H NMR, and the free energy of activation is measured as $\Delta G^{\ddagger}_{210}$ = 10.2 kcal/mol at a coalescence temperature of 210 K. Cavitand **5** forms inclusion complexes with 4-methylbezamide guests such as 4-methyl-*N*-*p*-tolylbenzamide **6** and *N*,4-dimethylbenzamide **7** in water-saturated $CDCl_3$. However, an isomorphic 4-methylanilide guest such as *N*-4-tolylacetamide **8** cannot be recognized in the concave cavity of **5**. This high selectivity toward 4-methylbenzamide over 4-methylanilide seems attributable to the hydrogen-binding interaction between the NH proton of 4-methylbezamide guest **7** and the oxygen atom of the closest water molecule.

Introduction

Extensive studies on resorcinarene-based cavitands have been performed in conjunction with recent advances in supramolecular chemistry, especially in selective molecular recognition, molecular switches, or molecular sensors, after its first introduction by Cram in 1982.[1−11] Cavitands are synthetic organic compounds with enforced

* To whom correspondence should be addressed at the Department of Applied Chemistry, Kyungpook National University.
† Department of Dyeing and Finishing, Kyungpook National University.
‡ Pusan National University.
§ Soongsil University.

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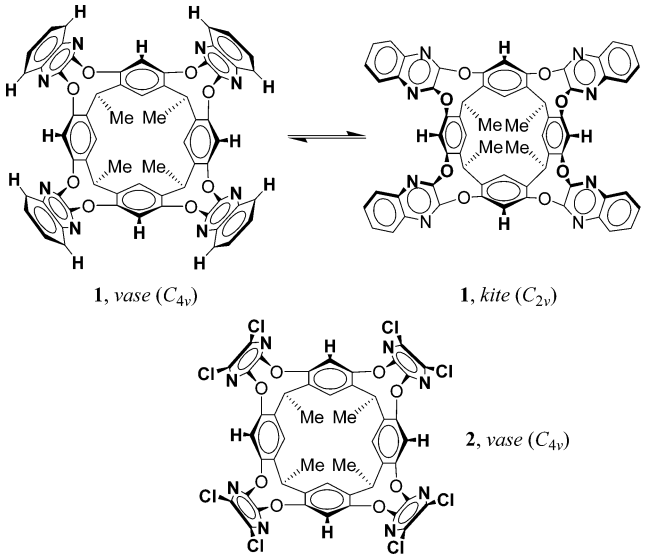

FIGURE 1. Conformational equilibrium between *vase* and *kite* conformers of cavitand **1** with four quinoxaline flaps and the *vase* conformer of cavitand **2** with four dichloropyrazine flaps.

concave cavities large enough to complex complementary organic compounds or ions.[2] The first cavitand **1** has four quinoxaline fractions bridged to two hydroxyl groups of adjacent resorcinol moieties of resorcin[4]arene. By flapping the quinoxaline moieties, the cavitand **1** has two bistable conformational states; *vase* and *kite* conformers, but the cavitand **2** with four dichloropyrazine flaps exists only as a vase conformer as shown in Figure 1. In cavitand **1**, the *vase* conformation was favorable above room temperature, but only the kite conformer was observed at temperature below 223 K.

According to Cram and co-workers, the conformational interconversion was rationalized by solvation−solvophobic effects. At low-temperature, solvation of the large and rigid quinoxaline surfaces of **1** favors the kite conformation but at higher temperature liberating solvent molecules from the surfaces the vase conformer with a few solvents in the cavity predominates by solvophobic effects, an entropy-driven process.[2,12] However, solvation stabilization on smaller pyrazine surfaces of cavitand **2** is insufficient to keep the kite conformation.

The controlled conformational interconversion of the quinoxaline cavitand analogue of **1** by protonation or metal coordination has been reported by Diederich and co-workers.[4] Protonation or metal ion coordination of the quinoxaline N-atoms favors kite conformation due to electrostatic repulsion of adjacent cationic sites. On the other hand, the stabilized vase conformations for inclusion phenomena have been also extensively studied by Rebek and co-workers. Self-folding cavitands by intramolecular hydrogen bonds between eight amide groups on the upper rim of cavitands are the most fascinating systems possessing the stabilized open-ended cavity.[13]

Rebek and our groups independently synthesized a new type of cavitand **5** possessing four benzimidazole flaps.[14a,15] Structural analysis and complexation with cations on cavitand **5** were excellently performed by Rebek and co-workers.[14a,b] We report here new observations on the complexation with neutral guests, the vase conformational stability with carboxylic acids, and annular tautomerism on cavitand **5** in $CDCl_3$.

Results and Discussion

Synthesis. Octanitro cavitand **3** and octaamino cavitand **4** first reported by Rebek were similarly prepared.[13] Reduction of **3** by catalytic hydrogenation with Raney nickel under hydrogen afforded octaamino cavitand **4**.[16] Treatment of the amine **4** with triethyl orthoformate in

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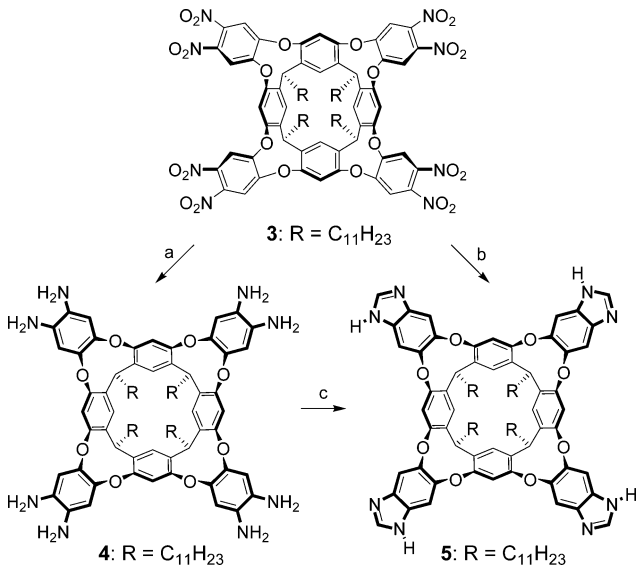
SCHEME 1[a]



[a] Reagents and conditions: (a) Raney Ni, H_2 (10 atm), PhMe, 45 °C, 16 h, 98%; (b) $SnCl_2 \cdot 2H_2O$, concd HCl/DMF (1:2), 120 °C, 21 h, 80%; (c) $HC(OEt)_3$, abs EtOH−AcOEt (1:1), reflux, 5 h, 83%.

absolute ethanol/ethyl acetate under reflux afforded benzimidazole cavitand **5** in 83% yield (Scheme 1). Complete reduction of eight nitro groups of **3** to amino groups of **4** was important to successfully obtain pure tetrabenzimidazole cavitand **5**. However, the method was not reliable and not reproducible due to instability of catalyst; thus, an alternative reduction method with stannous chloride in concd HCl was also used.[12,14a,16] However, the reduction of **3** with stannous chloride in DMF/concd HCl (2:1) directly afforded **5** in 73−80% yield without isolating the unstable octaamino cavitand **4**. The formation of benzimidazole from *o*-phenylenediamine in DMF presumably occurred via formyl group transfer from DMF to an amino group of the *o*-phenylenediamine moieties and consecutive condensation.[17]

Conformational Studies. Cavitand **5** was almost insoluble in nonpolar solvents such as $CDCl_3$ or toluene-d_8, and the proton NMR spectra have incomprehensible sets of broad resonances. However, the addition of small amounts of methanol to the suspension in $CDCl_3$ enhanced the solubility resulting in clean solution, and the signals of the NMR spectrum were sharpened. The spectrum with expected C_4 symmetry of **5** was almost invariant over a wide temperature range. Rebek clearly rationalized by molecular modeling and NMR experiments that the cavitand **5** forms a hollow C_{4v} symmetrical vase conformation as a result of intermolecular hydrogen bonding with four hydroxyl-containing molecules such as alcohols and water between the NH and N atoms of the neighboring benzimidazole fragments as shown in Figure 2.[14a]

The ^{1}H NMR spectrum of cavitand **5** in $CDCl_3/CD_3OD$ (9:1, v/v) shows one triplet for the methine protons of the bridges at 5.72 ppm, one singlet for the CH protons of the imidazole moieties at 7.73 ppm, one singlet for the protons of benzene ring in benzimidazole moieties at 7.59 ppm, and two singlets for the protons of the resorcinol rings at 7.46 and 7.17 ppm, whereas NH protons were not detected due to chemical exchange with CD_3OD solvent (Figure 3d). The chemical shift of the methine protons of the bridges is helpful to estimate the conformations of cavitands: the chemical shift in the C_{4v} symmetrical vase conformation appears at a lower field than 5.5 ppm, while that in the C_{2v} symmetrical kite conformation appears at a higher field than 4.0 ppm.[2]

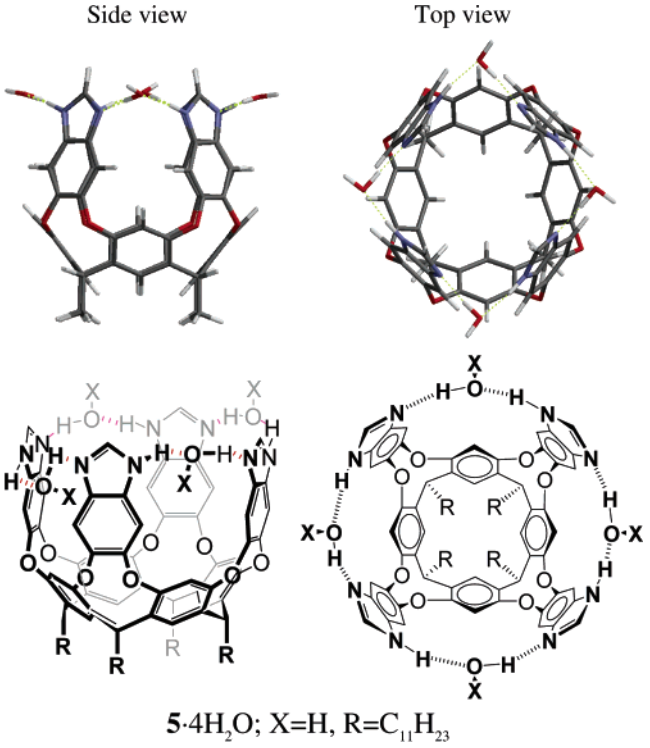


FIGURE 2. Energy-minimized structure of benzimidazole cavitand **5**·$4H_2O$ in tube representations (Spartan 04 V1.0.1, MMFF). The long alkyl chains replaced by methyls for clarity.

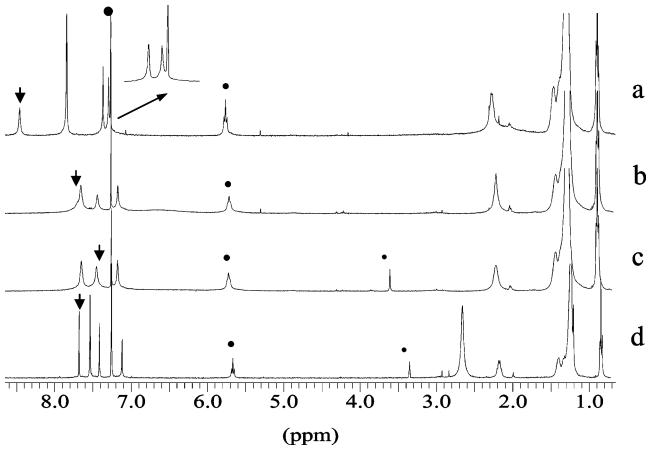


FIGURE 3. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 293 K) of (a) **5**·$4CF_3CO_2H$, (b) **5**·$4CH_3CO_2H$, (c) **5**·$4CH_3OH$, and (d) **5** in $CD_3OH/CDCl_3$ (1:9, v/v): (▼) CH protons of the imidazole moieties; (■) methine protons of the bridges; (◆) free methanol at 3.61 ppm in $CDCl_3$; (▽) residual solvent of CD_3OD; (●) residual solvent of $CDCl_3$.

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The ^{1}H NMR spectrum of benzimidazole cavitand **5** in $CDCl_3/CD_3OD$ (9:1, v/v) shows the characteristics for a C_{4v}-symmetrical vase conformation of cavitands. The spectra were almost invariable from 213 to 333 K, indicating that the vase conformation of cavitand **5** is very stable under these conditions.

The variation in the conformation of **5** due to interaction with the hydroxyl-containing molecules (HO−X) other than water (X = H) and methanol (X = CH_3) was investigated by ^{1}H NMR. Carboxylic acids such as acetic acid (X = CH_3CO) and trifluoroacetic acid (X = CF_3CO) could act as hydrogen-bond donor−acceptors between the NH and N atoms of the neighboring benzimidazole fragments. The cavitand **5** in $CDCl_3$/acetic acid (9:1) or $CDCl_3$/trifluoroacetic acid also showed a well-resolved ^{1}H NMR spectrum characteristic for a C_{4v} symmetric vase conformation, showing the methine protons in a range of 5.6−5.7 ppm. To obtain better spectra with higher signal-to-noise ratio, quantitative complexes of **5** with four HO−X molecules were prepared by evaporating the solvent from the above NMR tubes, drying the tubes under high vacuum at room temperature, and then adding dry $CDCl_3$ in the NMR tubes. Their ^{1}H NMR spectra taken at 293 K were characteristic for a C_{4v} symmetric vase conformation as shown in Figure 3. Under such drying conditions, volatile solvents and acetic acids could be completely removed, and the cavitand **5** complexes in the NMR tubes are considered as **5**·4HOX complexes in $CDCl_3$ because no free acetic acid or methanol molecule was observed in the ^{1}H NMR spectra even though a small amount of methanol was shown at 3.61 ppm in the spectrum c. The content of free methanol appeared at 3.61 ppm corresponds to only 6 mol % of **5**. The proton resonances of the complexed hydroxyl-containing molecules such as methanol and acetic acid are not seen in the spectrum probably due to broadened signals.

Compared to the NMR spectrum d of **5** in $CDCl_3/CD_3$-OD (9:1, v/v), the spectrum c of **5**·4CH_3OH in $CDCl_3$ is much broader and some resonances overlapped. Spectrum c from 293 K shows three signals instead of four signals expected in the aromatic region: one singlet for the protons of benzene ring in benzimidazole moieties at 7.65 ppm and two singlets for the protons of the resorcinol rings at 7.17 and 7.46 ppm. The missing CH protons of the imidazole moieties were revealed as overlapped with the signal at 7.46 ppm by integration and also confirmed from the spectrum at 283 K which shows a new broad resonance at 7.50 ppm for the CH protons. Spectrum b of cavitand **5**·4CH_3CO_2H in $CDCl_3$ is similarly broad with that of **5**·4CH_3OH in $CDCl_3$, but the CH resonance of the imidazole moieties shifts to downfield 7.73 ppm at 293 K. However, the spectrum of the cavitand **5**·4CF_3CO_2H in $CDCl_3$ is sharp and well-resolved showing a sharp singlet at 8.46 ppm for the CH protons of the imidazole moieties. As shown above, the chemical shifts of the CH protons of the imidazole moieties were very susceptible in the conditions. Therefore, the chemical shifts of the CH protons were plotted over the temperature. Figure 4 records the ^{1}H NMR methine signal changes with temperature from 223 to 333 K of **5**·4HOX complexes.

The CH signal of each **5**·4HOX complex gradually shifts to upfield within the range of 0.4 ppm as the temperature is raised. However, the large chemical shift

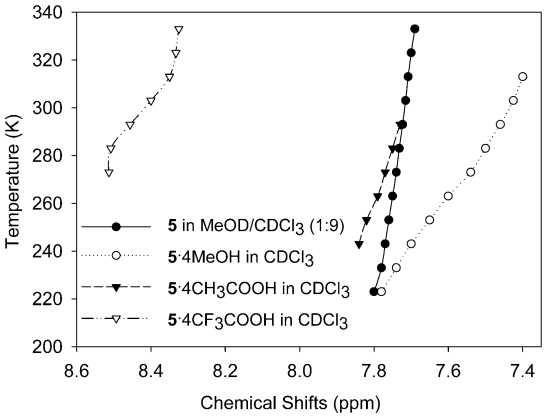

FIGURE 4. Effect of temperature changes in the ^{1}H NMR chemical shifts of the CH protons in the imidazole moieties of **5**·4HOX complexes.

difference is noticeable as much as 1.0 ppm between **5**·4CF_3CO_2H and **5**·4CH_3OH. The CH chemical shifts for **5**·4CH_3OH, **5**·4CH_3CO_2H, and **5**·4CF_3CO_2H were observed at 7.46, 7.73, and 8.46 ppm at 293 K, respectively. This chemical shift sequence for the CH protons of the imidazole moieties in the **5**·4HOX complexes is parallel with the acidity of the hydroxyl-containing molecules such as CF_3CO_2H, CH_3CO_2H, and CH_3OH. The hydrogen-bond donor and acceptor strength of HOX, comparable with their acidity, could affect the stability of the **5**·4HOX complex.[19,20] The hydrogen bonding of the hydroxyl proton of HOX to the lone pair in the sp^2 orbital of the N atom in the imidazole ring would affect decreasingly the π electron density of the imidazole ring, resulting in deshielding of the CH proton of the imidazole ring. The stronger the hydrogen bond donor strength of the HOX is, the stronger hydrogen bonds of HOX between the NH and N atoms of the neighboring benzimidazole fragments can be formed[20] and the more the CH protons of the imidazole ring are deshielded. Therefore, the chemical shift of the CH proton of the imidazole ring can be informative for determining the stability of the vase conformation of **5**.

The vase structure of **5**·4CF_3CO_2H withstands up to 333 K in $CDCl_3$. The ^{1}H NMR signals of **5**·4CF_3CO_2H in $CDCl_3$ were very sharp at 333 K but became broadened below 273 K. The spectrum from 333 K shows a triplet for the methine protons at 5.81 ppm, one singlet for the CH protons of the imidazole moieties at 8.32 ppm, one singlet for the benzene protons of benzimidazole moieties at 7.80 ppm, and two singlets for the protons of the resorcinol rings at 7.33 and 7.32 ppm. Similarly, the proton signals of **5**·4CH_3CO_2H in $CDCl_3$ were broadened above 313 K, but the triplet for the methine protons at 333 K was observed at 5.71 ppm indicative for the vase structure of **5**. However, the vase structure of cavitand **5**·4CH_3OH is destroyed above 323 K and could not be reformed upon cooling the NMR sample because it

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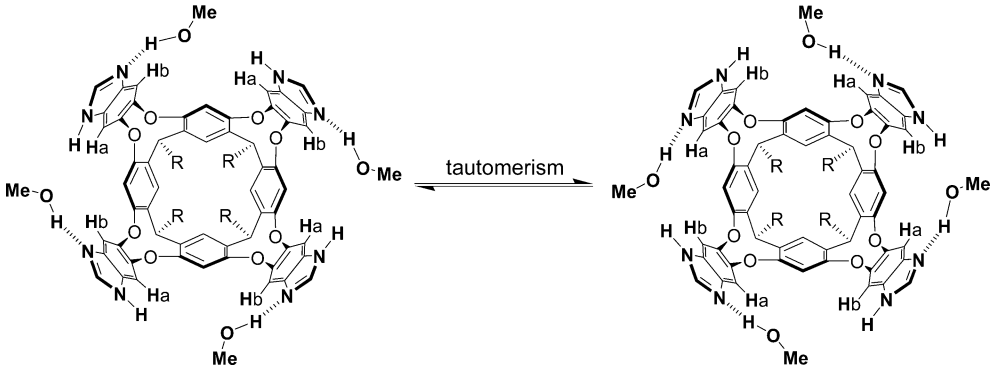


FIGURE 5. Proposed hydrogen-bonding patterns of two tautomers of cavitand **5**·4CH_3OH.

precipitated out in $CDCl_3$. It suggests that the process is irreversible and the released free methanol molecules could not effectively reconstruct the vase structure by forming intermolecular hydrogen bonds between the NH and N atoms of the neighboring benzimidazole fragments.

In the presence of excess carboxylic acid or methanol, the cavitand **5** in $CDCl_3$ maintains kinetically stable C_{4v} vase conformation, indicating the triplet for the methine protons of the bridges at 5.64−5.75 ppm over the whole temperature-solvent range from 198 to 333 K. Also, the vase structures are observed for the cavitand complexes **5**·4CF_3CO_2H, **5**·4CH_3CO_2H, and **5**·4CH_3OH in $CDCl_3$, showing the triplets at 5.61−5.81 ppm from 243 to 333 K, 5.63−5.74 ppm from 223 to 333 K, and 5.59−5.75 ppm from 198 to 323 K, respectively.

The systems between XOH acids and N bases with lone-pair electrons are the typical hydrogen-bonding systems existing in two different proton-limiting structures, XO−H···N ↔ XO^- $H-N^+$, which yield hydrogen-bonding and ionic interactions, respectively. From the observed results of the stable vase structures of **5**·4HOX, these systems between N atoms of benzimidazole moieties of **5** and XOH molecules seem to belong to the XOH···N hydrogen bonding, which stabilizes the vase conformation, rather than the XO^- $H-N^+$ ionic interaction, which might destabilize the vase conformation probably by solvation of ions.[20] The stronger hydrogen bond donor strength of the hydroxyl-containing molecule could better stabilize the vase structure of the complex **5**·4 HO-X in $CDCl_3$ in the order of their acidity: CF_3-COOH > CH_3COOH > CH_3OH.

Annular Tautomerism. Two symmetrically different protons of the benzene ring in the benzimidazole moieties of cavitand **5** were observed as isochronous at room temperature in a 400 MHz ^1H NMR spectrometer, showing a singlet at 7.59 ppm in $CDCl_3/CD_3OD$ (9:1). These protons exchange each other faster than the NMR time scale and are an uncoupled two-site exchange case in dynamic NMR spectroscopy.

Dynamic NMR spectroscopy allows us to observe the change occurring in reactions with rate constants k in the range from about 10^{-1}−10^3 s^{-1}, corresponding to $\Delta G^{\ddagger}$ between 5 and 23 kcal/mol, respectively.[18] Therefore, the observed low energy, rapid-exchange process under normal conditions becomes a slow process if the temperature was sufficiently lowered, and was often observed by ^1H dynamic NMR spectroscopy. If the hydrogen bonds exist intermolecularly between methanol and the benzimidazole moiety as depicted in Figure 5, the donor protons OH of methanol molecules and the NH protons of imidazole moiety are anisochronous, and two different protons of the benzene ring in the benzimidazole moieties of cavitand **5** would be distinguishable below the low temperature at which the exchange process is sufficiently slower than NMR time scale. If this process takes place with directionalty in back-and-forth, the exchange process can be explained by the annular tautomerism as shown in Figure 5.[21] It is structurally and sterically reasonable that the exchange process can occur with the directionality when considering the cyclic array pattern of the intermolecular hydrogen bonding with four methanol molecules between the NH and N atoms of the neighboring benzimidazole fragments of **5**.

Two aromatic protons H_a and H_b of cavitand **5** appear at 7.59 ppm as a sharp singlet at room temperature, but the signal were gradually broadened as the temperature was lowered. Lowering the temperature below 203 K leads to a splitting of the signals, and these signals become resolved by 52 Hz at 7.69 and 7.56 ppm at 198 K as shown in Figure 6. To obtain the kinetic parameters at slow-exchange limit, the NMR sample of **5** in $CDCl_3/CD_3OD$ (9:1, v/v) was further cooled, but frozen below 195 K.

At a coalescence temperature (T_c) of 210 K, the rate constant, k_{210} of the annular tautomerism is calculated to be 113/s by the coalescence temperature method, and free energy of activation, $\Delta G^{\ddagger}_{210}$ of this process is corresponding to 10.2 kcal/mol. Although the $\Delta G^{\ddagger}_{210}$ is obtained using $\Delta\nu = 52$ Hz, the separation between the two signals at 198 K, which is above the slow-exchange limit, the value is reliable because the accuracy of free energy of activation is much dependent on T_c rather than $\Delta\nu$ in the coalescence temperature method. The main source of error is the temperature, unless $\Delta\nu$ is small. A reasonable error ±2 K in T_c corresponds to an error in $\Delta G^{\ddagger}_C$ of ±0.1 kcal/mol.[18]

The energy required breaking four hydrogen bonds between the proton of methanol and N atom of the imidazole moiety of **5** corresponds to the free energy of activation, $\Delta G^{\ddagger}_{210}$, of 10.2 kcal/mol, which leads to an estimate of 2.55 kcal/mol for the strength of this hydrogen bond N···H−O−R which is comparable but less than the calculated values of 6.16 and 7.81 kcal/mol for the

(21) Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Böhmer, V. *Chem. Eur. J.* **2001**, *7*, 4403.

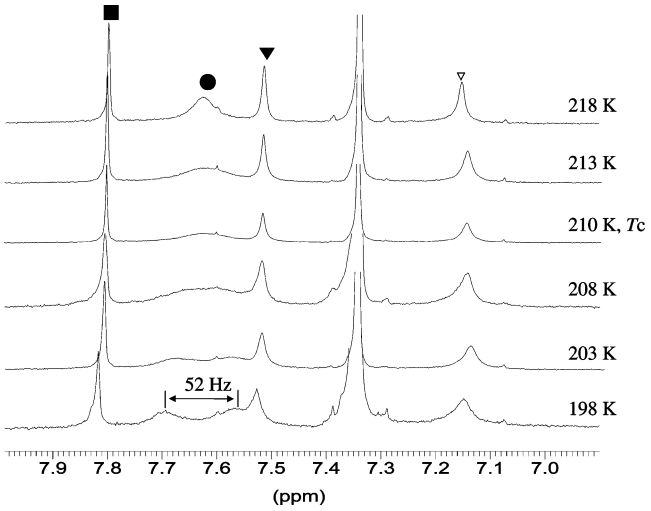


FIGURE 6. 400 MHz ^{1}H NMR spectra of benzimidazole cavitand **5** in $CDCl_3/CD_3OD$ (9:1, v/v): (■) CH protons of the imidazole moieties; (●) benzene protons of benzimidazole moieties; (▼ and ▽) benzene protons of the resorcinol moieties.

corresponding hydrogen bonds for pyridine−formic acid and pyridine−acetic acid systems, respectively.[20]

Selective Recognition toward 4-Methylbenzamide over 4-Methylanilide. The vase structures of the cavitand **5**·4HO-X have a hollow cavity able to accommodate guest molecules. The formations of the stable inclusion complexes of 2-methylimidazole analogue of **5** with tetramethylammonium and phosphonium cations in water-saturated $CDCl_3$ or in DMF-d_7 have been reported by Rebek and co-workers.[14a,b] Analogous cavitands such as pyrazinimide and phenyleneurea cavitands have been also reported to form self-assembled capsules. The guest, 4-methyl-*N*-4-tolylbenzamide, **6** was used as a template molecule to form the cylindrical bimolecular capsules in mesitylene-d_{12}.[16,22]

Complexation of cavitand **5** with the guest **6** was performed in similar conditions. The 400 MHz ^{1}H NMR spectrum of **5** in CD_3OD/mesitylene-d_{12} (4 mM, 1:19, v/v) exhibits sharp signals at room temperature and is characteristics for a C_{4v} symmetrical vase conformation showing a triplet for the methine protons of the bridges at 6.12 ppm, one singlet for the CH protons of the imidazole moieties at 7.50 ppm, one singlet for benzene protons of benzimidazole moieties at 7.28 ppm and two singlets for the protons of the resorcinol rings at 7.48 and 7.20 ppm. When 5-fold excess of guest **6** was added to **5**, a new broad signal was barely observed at −2.98 ppm at room temperature. The broad upfield signal continuously changes into a sharp singlet as the temperature is lowered from 323 to 223 K (Figure 7d). Due to strong signals of excess guest **5** and high residual protons of commercial mesitylene-d_{12} NMR solvent, the chemical shift assignment and the evaluation of the stability constant on the complex of **5** with guest **6** were hampered, but the complex has a 1:1 stoichiometry and is kinetically stable on the NMR time scale in the temperature range 223−323 K. The large upfield shifted singlet is a consequence of the *p*-methyl group of the guest **6** enclosed in the cavity of the cavitand by an attractive $CH_3-\pi$ interaction. The induced large upfield shift ($\Delta\delta = -5.1$ ppm) indicates close proximity of the methyl group to the shielding regions of the cavitand aryl rings. It should be emphasized that only one kind of methyl group of the two kinds of methyl groups in guest **5** is noticed in the upfield.

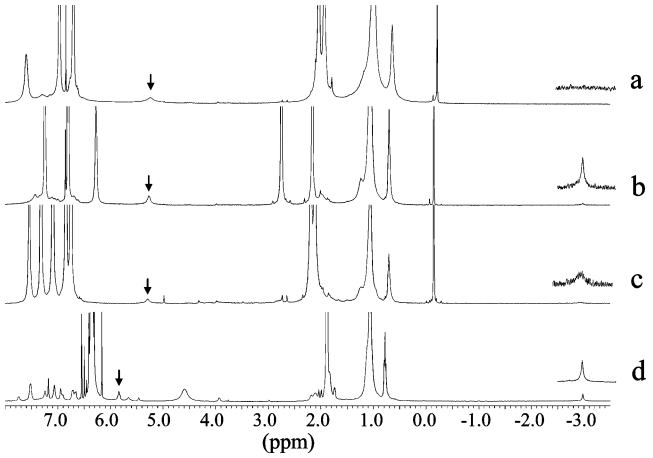
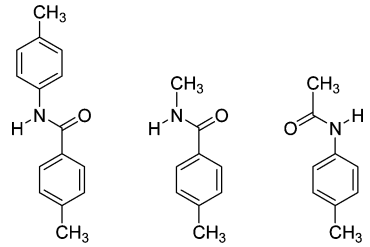


FIGURE 7. ^{1}H NMR spectra of (a) 4 mM **5** + 20 mM **8** in water-saturated $CDCl_3$ at 223 K, (b) 4 mM **5** + 20 mM **7** in water-saturated $CDCl_3$ at 233 K, (c) 4 mM **5** + 20 mM **6** in water-saturated $CDCl_3$ at 233 K, and (d) 4 mM **5** + 20 mM **6** in CD_3OD/mesitylene-d_{12} (1:19) at 233 K; (▼) methine protons of the bridges; the enlarged signals at ∼−2.9 ppm from the guests enclosed in the cavity of cavitand **5**.

CHART 1. Structures of Guests, 4-Methyl-*N*-4-tolylbenzamide (6), *N*,4-Dimethylbenzamide (7), and *N*-4-Tolylacetamide (8)



In water-saturated $CDCl_3$ solvent the similar complexation phenomenon was observed except for somewhat broad signal of complexed guest (Figure 7c). Even under the extreme condition of 50-fold excess **6**, only one singlet from the inclusion guest **6** occurred in the upfield. This high selectivity for one of the two possible diastereomeric complexes between cavitand **5** and guest **6** was examined by performing the complexation experiments with *N*,4-dimethylbenzamide **7** and *N*-4-tolylacetamide **8** in water-saturated $CDCl_3$, which are two amide fractions of **6** (Chart 1). A mixture of **5** and **7** (4 mM/20 mM, respectively) in water-saturated $CDCl_3$ at 273 K gave a broad signal at −2.90 ppm which was sharpened and shifted to −2.96 ppm at 233 K (Figure 7b). However, the similar mixture of **5** and **8**, and even 50-fold excess of **8**, in water-saturated $CDCl_3$ at 223 K showed no signals in the upfield region consequent upon the complexation of **5** with **8** (Figure 7a). We conclude that cavitand **5** can

(22) (a) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **1998**, *394*, 764. (b) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1136. (c) Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 187.

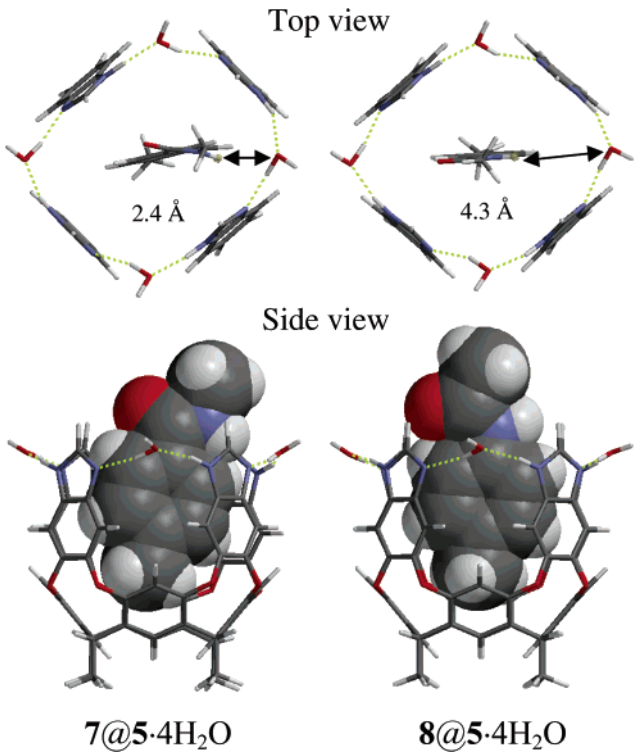


FIGURE 8. Energy-minimized structures of **7@5**·$4H_2O$ and **8@5**·$4H_2O$ (Spartan 04, V1.0.1, MMFF). The closest distances of N−H···OH_2 are measured as 2.40 Å in **7@5**·$4H_2O$ and 4.31 Å in **8@5**·$4H_2O$, and the angles between the molecular axis of guest through aromatic moiety and the axis of the molecular cavity are 5 and 12 degree in **7@5**·$4H_2O$ and **8@5**·$4H_2O$, respectively. For clarity, long pendant chains are replaced by methyls in side views and resorcinarene moieties of **5** are omitted in top views.

selectively complex with **7** over **8**. The high selectivity of cavitand **5** toward **7** is an unexpected observation, and furthermore, the kinetically stable complex of cavitands with neutral organic guests in $CDCl_3$ on the NMR time scale is first observed, even though cavitand **1** weakly complexes with nonpolar aromatic compounds in polar acetone.[3a] The cavitand hosts have a nonpolar concave surface which does not strongly complex with organic guests in a small and lipophilic solvent like $CDCl_3$. Small nonpolar solvent molecules can solvate the interior of the cavity and compete with guests to fill the cavity. The binding between cavitand **1** and nonpolar aromatic guests was attributed to an attractive $CH_3-\pi$ interaction and dipole−dipole interations.[3a] However, these interactions cannot explain the high selectivity of **5** toward **7** over **8** which are sterically almost isomorphic, but structurally different in terms of dipole moment and hydrogen bonding pattern. Cavitand **5** has additional polar groups on the rim of the cavity such as NH and N atoms of benzimidazole fragments and four water molecules, which significantly affect for the complexation with the guests with secondary amide functionality.

Energy-minimized structures of **7@5**·$4H_2O$ and **8@5**·$4H_2O$ are shown in Figure 8. The plane of the amide group of guest is almost parallel with the line connecting two crossing water molecules in each complex (in top view). The tolyl group in each complex is completely immersed in the cavity, and the amide fraction is just above the plane of four water molecules (in side view). Therefore, the methyl groups are similarly located deeply in the cavity at 3.00 and 3.03 Å above the plane connecting four carbons at the 5-position of the resorcinol rings of **7@5**·$4H_2O$ and **8@5**·$4H_2O$, respectively. The noticeable structural difference between **7@5**·$4H_2O$ and **8@5**·$4H_2O$ is that the molecular axis of the guest **7** of **7@5**·$4H_2O$ is tilted about 12 degree from the axis of the molecular cavity, but the axis **8** of **8@5**·$4H_2O$ is almost parallel, tilted about 5° to the axis of the molecular cavity. The large tilt is apparently caused by the result of the hydrogen bonding interaction between the NH proton of amide guest **7** and the oxygen atom of the closest water molecule, which are separated only by 2.40 Å. The corresponding hydrogen bonding between **5** and **8** is absent. This small difference of hydrogen bonding seems sufficient to discriminate the isomorphic guests **7** and **8** considering hydrogen bonding energy 3 to 5 kcal/mol which is corresponding to the association constant 2.5×10^2 to 1.0×10^4 at 273 K.

Summary

Cavitand **5** with four benzimidazole flaps is directly synthesized by reducing octanitro cavitand **3** having *o*-dinitrobenzene moieties with $SnCl_2 \cdot 2H_2O$ in DMF/concd HCl presumably via formylation to the amino group of the *o*-phenylenediamine moieties and consecutive condensation. Cavitand **5**·4HOX (X = Me, CH_3CO, or CF_3-CO) with enforced concave cavity can be formed by intermolecular hydrogen bonding with four hydroxyl-containing molecules, HOX, such as methanol, acetic acid, and trifluoroacetic acid. The vase structure of **5**·4HOX is kinetically stable on the NMR time scale, and the stability of the vase structure is dependent on hydrogen-bond donor strength of the HOX which is comparable with their acidity. The stronger the hydrogen-bond donor strength of X−OH is, the stronger hydrogen bonds are formed between the NH and N atoms of the neighboring benzimidazole fragments, which stabilize the vase conformation of cavitand **5**. The annular tautomerism of **5** as a result of the proton exchange between NH and N atoms of the neighboring benzimidazole fragments is observed by the proton relay of methanol molecule in $CDCl_3/CD_3OD$ (9:1, v/v). The free energy of activation, $\Delta G^{\ddagger}$ for the tautomerism is measured as 10.2 kcal/mol at coalescence temperature of 210 K, leading to an estimate of 2.55 kcal/mol for the strength of the hydrogen bond N···H−OMe between N atom of benzimidazole and OH proton of methanol. Cavitand **5**·$4H_2O$ with enforced concave cavity selectively forms an inclusion complex with 4-methylbenzamide **7** over 4-methylanilide **8** in water-saturated $CDCl_3$. The hydrogen binding interaction between the NH proton of amide guest **7** and the oxygen atom of the water molecule bound to cavitand **5** seems to play a role in the selective recognition toward 4-methylbenzamide over 4-methylanilide.

Experimental Section

General Remarks. All commercially obtained solvents and reagents were used as purchased. *N,N*-Dimethylformamide (DMF) was obtained as anhydrous, 99.8% grade. NMR data were obtained at 400 MHz for proton and at 100 MHz for carbon in the indicated solvent. Chemical shifts (δ) were

recorded in ppm using either relative to TMS or residual undeuterated solvent and coupling constants in hertz (Hz). The fast atom bombardment (FAB) mass spectra were obtained on a double-focusing high-resolution mass spectrometer using a xenon gun and NOBA matrix. Column chromatography was performed on silica gel (70−230 mesh). Octanitro cavitand **3** and octaamino cavitand **4** are prepared as described in previous disclosures.[16]

8,10,12,14-Tetraundecyl-6,16:7,15-dimetheno-1*H*,8*H*,10*H*,12*H*,14*H*,19*H*,27*H*,35*H*-benzimidazo[5″,6″:2′,3′][1,4]-benzodioxonino[10′,9′:5,6]benzimidazo[5″,6″:2′,3′]benzimidazo[5‴,6⁗:2‴,3‴][1,4]dioxonino[6‴,5‴:9′,10′][1,4]benzodioxonino[6′,5′:9,10][1,4]benzodioxonino[2,3-*f*]benzimidazole (Benzimidazole Cavitand 5). Method A. A mixture of octanitro cavitand **3** (388 mg, 0.22 mmol), tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$, 2.0 g), concd HCl (8 mL), and DMF (16 mL) was heated at 120 °C for 21 h. The reaction mixture was poured into ice−water (100 mL). The precipitate was collected by filtration, washed with water (20 mL × 3), and dried. The product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to give the product (275 mg, 80%) as an ivory solid.

Method B. To a solution of octaamino cavitand **4** (400 mg, 0.26 mmol) in ethyl acetate (10 mL) and absolute ethanol (10 mL) was added triethyl orthoformate (0.26 mL, 1.56 mmol) by a syringe under nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h and concentrated under reduced pressure. The residue was purified by a column chromatography to give the product (337 mg, 83%): mp > 250 °C; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 9:1) δ 7.73 (s, 4H), 7.59 (s, 8H), 7.46 (s, 4H), 7.17 (s, 4H), 5.72 (t, 4H, J = 8.2 Hz), 2.23 (dd, 8H), 1.46−1.21 (br m, 72H), 0.89 (t, J = 7.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$ = 9:1) δ 156.1, 150.0, 142.0, 135.3, 134.2, 123.4, 116.8, 109.5, 33.5, 32.5, 32.1, 29.9, 29.5, 28.2, 24.8, 22.8, 14.2; IR (KBr) 3387 (NH stretch), 2925, 2853, 1486, 1462, 1346, 1269 cm^{-1}; FAB MS (NOBA) *m/z* 1560.93 (33), 1561.93 (100), 1562.92 (98), 1563.93 (57), calcd for $C_{100}H_{120}N_8O_8$ *m/z* 1560.9229. Anal. Calcd for $C_{100}H_{120}N_8O_8$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.61; H, 7.83; N, 7.24.

General Procedure for Preparation of Cavitand 5·4HOX NMR Samples. The cavitands with four equivalent HOX complex **5**·4HOX (X = Me, CH_3CO, and CF_3CO) were prepared by shaking NMR tubes containing a mixture of cavitand **5** (4.0 mg) in HOX/$CHCl_3$ (1:9, 0.5 mL) for 10 min, followed by evaporating solvents under reduced pressure and drying the NMR tubes under high vacuum at room temperature until constant weight (usually for 3 h). The residues were dissolved by adding $CDCl_3$ (0.5 mL) into the NMR tube.

NMR Studies. The purity of the NMR solvents was as follows: mesitylene-d_{12} 98 atom % D; methanol-d_4 99.8+ atom % D, and chloroform-d 99.9 atom % D. A stock solution (4.0 mM) of cavitand **5** was prepared by drying a flask containing 18.74 mg (0.012 mmol) of cavitand **5** in a glass tube oven at 100 °C under high vacuum for 12 h, followed by fitting a rubber septa to the flask under nitrogen and adding water-saturated $CDCl_3$ (3.0 mL) via a syringe. The mixture was well stirred by a vibrator. In CD_3OD/mesitylene-d_{12} (1:19, v/v), ^{1}H NMR spectra were obtained for 4 mM cavitand **5** with excess 4-methyl-*N*-4-tolylbenzamide **6** (5-fold to 50-fold excess) at temperatures from 223 to 273 K. In water-saturated $CDCl_3$, ^{1}H NMR spectra were obtained for 4 mM cavitand **5** with excess guests such as *N*,4-dimethylbenzamide **7** (5-fold excess) and *N*-4-tolylacetamide **8** (5-fold to 50-fold excess) at temperatures from 223 to 273 K.

Determination of Kinetic Parameters for the Annular Tautomerism.[18] ^{1}H NMR spectra of 5 mM benzimidazole cavitand **5** were taken from 198 to 323 K in $CD_3OD/CDCl_3$ (1:9, v/v). The kinetic parameters for the annular tautomerism of tetrabenzimidazole cavitand **5** were determined by coalescence temperature (T_C) method. The first-order rate constant (k_C) was calculated with eq 1.

$$k_C = \pi\Delta\nu/\sqrt{2} = 2.22\ \Delta\nu \quad (1)$$

Also, the activation energy ($\Delta G^{\ddagger}_C$) was calculated with eq 2.

$$\Delta G_C^{\ddagger} = 4.58 T_C\left[9.972 + \log\left(\frac{T_C}{\Delta\nu}\right)\right] \times 10^{-3}\ \text{kcal mol}^{-1} \quad (2)$$

where $\Delta\nu$ is the separation in Hz between the two signals at slow-exchange limit and T_C is the coalescence temperature.

Molecular Modeling. Low energy conformations were determined by molecular mechanics with Monte Carlo minimization procedures using the MMFF94 force field. The equilibrium geometry for the low energy conformations was calculated at MMFF level.

Acknowledgment. We are grateful to the Basic Research Program of the Korea Science & Engineering Foundation (Grant No. 2001-12300-005-3) for financial support.

Supporting Information Available: The stacked NMR spectra of **5**·4HOX at various temperatures and for complexation experiments of cavitand **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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