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# Hydrazide as a New Hydrogen-Bonding Motif for Resorcin[4]arene-Based Molecular Capsules

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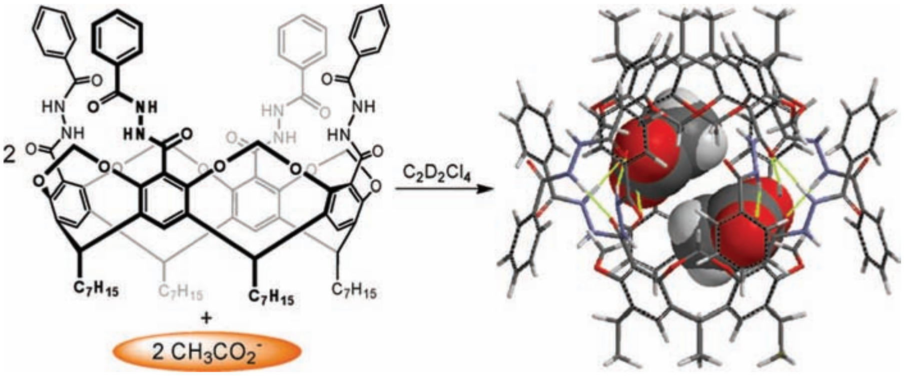
## ABSTRACT



**The resorcin[4]arene-based benzoylhydrazide cavitands formed stable molecular capsules in nonpolar solvents by the eight intermolecular N−H···*O*=C hydrogen bondings, two from each four paired hydrazides, and the four intramolecular O−$H_2C$−O···H−N hydrogen bondings on each cavitand. The stability of these molecular capsules depends on the encapsulated guest in the following order: $CH_3SO_3^-$ > $CH_3CO_2^-$ > $CH_3CH_2NH_2{\cdot}HCl \approx CH_3NH_2{\cdot}HCl$ > $(CH_3)_4N^+$ > toluene > $C_2D_2Cl_4$.**

Self-assembling molecular capsules based on noncovalent interactions have attracted considerable interest due to their potential as molecular storage, sensor, catalysts, or reaction chambers in the field of supramolecular chemistry.[1] Various examples of dimeric molecular capsules by hydrogen bonds such as Rebek's urea capsule[2] and imide capsule[3] are known to encapsulate a variety of neutral and cationic guests.[4] However, the recognition of anions by a neutral molecular capsule are quite limited.[5] Here, we report the versatile

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molecular capsules $\mathbf{1}_2$ using hydrazide as hydrogen-bonding motif and their recognition for anion as well as cation and neutral guests.

The benzoyl hydrazide-based hydrogen-bonding motif whose dimerization binding constant $K_{\mathrm{assoc}}$ was known to be ~$10^2$ $\mathrm{M}^{-1}$ in $CDCl_3$ at room temperature[6] was introduced on the upper rim of the $-O-CH_2-O-$ bridged resorcin[4]arene. The energy-minimized structure of molecular capsule $\mathbf{1a}_2$ using Spartan'04 V1.03 (Molecular Mechanics MMFF) (Figure 1) showed a well-defined molecular capsule with a ~200 Å$^3$ cavity which was stabilized systematically by the eight intermolecular $N-H_a\cdots O=C$ hydrogen bondings, two from each four paired hydrazides, and the eight intramolecular $N-H_b\cdots OArR$ hydrogen bondings, four from each two cavitands.[7]

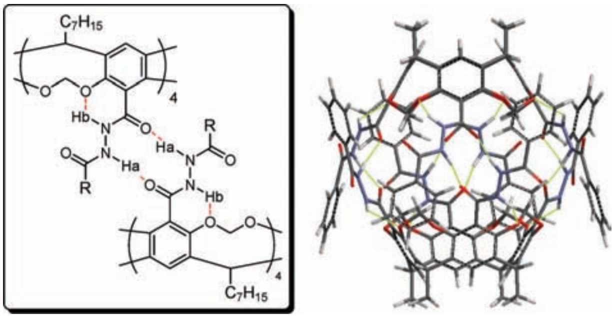
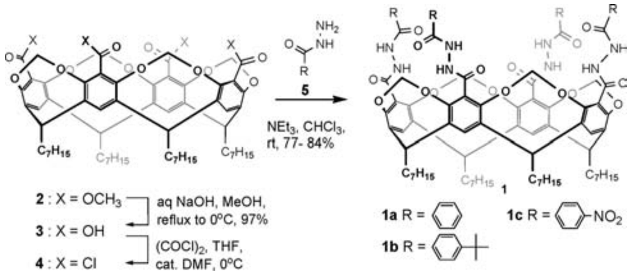


**Figure 1.** Hydrogen-bonding mode between a pair of hydrazides and the tubular model presentation of self-assembled molecular capsule $\mathbf{1a}_2$ (heptyls are exchanged with methyls for clarity).

Benzoylhydrazidocavitand **1** was synthesized from tetraester cavitand **2**.[8] Cavitand **2** was readily hydrolyzed by sodium hydroxide to give tetracarboxylic cavitand **3** in 97% yield. Treatment of cavitand **3** with oxalyl chloride and catalytic amount of DMF at 0 °C followed by removal of the solvent gave acid chloride cavitand **4**, which was reacted with commercially available benzoic hydrazide derivatives **5** in the presence of triethylamine at room temperature to afford the cavitands **1** in 77−84% yield (Scheme 1). All of the cavitands **1** were fully characterized with $^1$H NMR, $^{13}$C NMR, IR, high-resolution MALDI-TOF mass, and elemental analyses.

**Scheme 1.** Synthesis of Molecular Capsule **1**



Cavitands **1** were barely soluble in a pure nonpolar solvent such as $CH_2Cl_2$, $CHCl_3$, *p*-xylene, or mesitylene but very soluble in $C_2H_2Cl_4$, DMF, or DMSO.

The $^1$H NMR spectrum of cavitand **1a** in $C_2D_2Cl_4$ showed two singlets for the N-*H* protons at 8.89 and 8.81 ppm in the downfield region (Figure 2a), which showed no significant concentration dependence ($\Delta\delta < 0.03$ ppm). In contrast, for *N*-hexanoylbenzohydrazide, the dilution experiments (20 mM to 0.1 mM) in $C_2D_2Cl_4$ showed the upfield shift of the N-*H* peak from 8.74 to 7.83 ppm ($\Delta\delta = 0.91$ ppm). The FT-IR spectrum of **1a** in $C_2D_2Cl_4$ ($4 \times 10^{-3}$ M) showed a hydrogen-bonded, broad N-*H* stretching band of the benzoyl hydrazide group at 3195 cm$^{-1}$, while the FT-IR spectrum of *N*-hexanoylbenzohydrazide showed the N-*H* stretching band at 3410 cm$^{-1}$ under the same conditions.

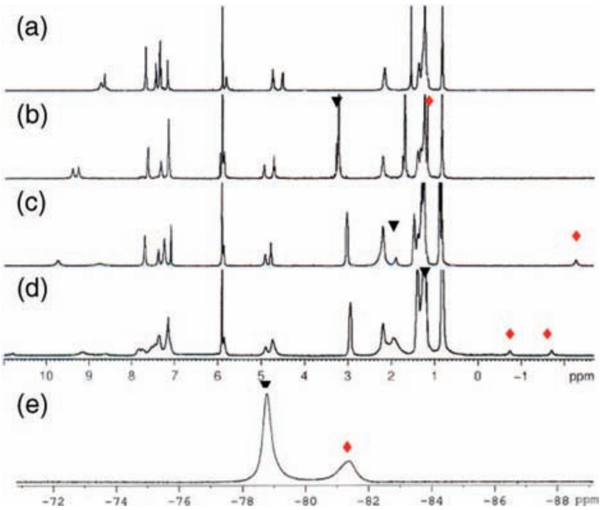


**Figure 2.** $^1$H NMR (400 MHz, (a−d)) and $^{19}$F NMR (282 MHz, (e)) spectra in $C_2D_2Cl_4$ at 297 K: (a) $C_2D_2Cl_4@\mathbf{1a}_2$ (2 mM), (b) $C_2D_2Cl_4@\mathbf{1a}_2$ + 4 equiv of $(CH_3)_4NCl$, (c) $C_2D_2Cl_4@\mathbf{1a}_2$ + 4 equiv of $CH_3CO_2NBu_4$; (d) $C_2D_2Cl_4@\mathbf{1a}_2$ + 4 equiv of $(CH_3)_2CH$-$CO_2NBu_4$, (e) $C_2D_2Cl_4@\mathbf{1a}_2$ + 6 equiv of $CF_3SO_3NBu_4$; ▼ = Me of free guest, ◆ = Me of encapsulated guest.

These results indicate the formation of a molecular capsule $C_2D_2Cl_4@\mathbf{1a}_2$ in $C_2D_2Cl_4$. When toluene was added to the $C_2D_2Cl_4$ solution of **1a**, a singlet at 0.02 ppm ($\Delta\delta = 2.28$ ppm) corresponding to the peak of methyl of the encapsulated toluene appeared and unchanged up to 60 °C. But it disappeared upon the addition of a protic solvent which collapses capsular structure.

Encapsulation phenomena of molecular capsule $\mathbf{1}_2$ were studied by $^1$H and $^{19}$F NMR spectroscopies in $C_2D_2Cl_4$ solution at room temperature. The addition of 4 equiv of various guests such as cation, anion, or neutral guest to this molecular capsule solution gave new signals corresponding to the protons of the encapsulated guest (Figure 2b−d). The

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ammonium salts such as $CH_3NH_2$•HCl and $CH_3CH_2NH_2$•HCl by itself are scarcely soluble in $C_2D_2Cl_4$, but they were encapsulated upon the contact with $C_2D_2Cl_4$@**1a**$_2$, which shows the capsule **1a**$_2$ prefers polar guests to $C_2D_2Cl_4$. In $^1$H NMR spectra, new signals appeared at 1.90 ppm and at 2.16 and 0.47 ppm for the encapsulated $CH_3NH_2$•HCl and $CH_3CH_2NH_2$•HCl, respectively. For $(CH_3)_4NCl$, the resonance signal of methyl protons of the encapsulated $(CH_3)_4N^+$ ion appeared at 1.15 ppm ($\Delta\delta = 2.06$ ppm) (Figure 2b). Stoichiometry by direct integration was one encapsulated ammonium ion per a capsule **1a**$_2$.

For anionic guests of $CH_3CO_2NBu_4$, $CH_3SO_3NBu_4$, or $CH_3OSO_3NBu_3CH_3$ whose cations are too large to fit in the capsule, the resonance signals of methyl protons of the encapsulated anions appeared at $-2.31$ ppm ($\Delta\delta = 4.26$ ppm, Figure 2c), $-1.56$ ppm ($\Delta\delta = 4.08$ ppm), and $-0.02$ ppm ($\Delta\delta = 3.72$ ppm), respectively. The $^1$H NMR titration experiment (400 MHz, $C_2D_2Cl_4$, 297 K) showed the slow guest exchange on the $^1$H NMR time scale and the fast pairwise complexation of two small anions ($2CH_3CO_2^-$@**1a**$_2$, $2CH_3SO_3^-$@**1a**$_2$, and $2CH_3OSO_3^-$@**1a**$_2$). When 1 equiv of $CH_3SO_3NBu_4$ in $C_2D_2Cl_4$ was added to $C_2D_2Cl_4$@**1a**$_2$ (2 mM), the ratio of $2CH_3SO_3^-$@**1a**$_2$/$C_2D_2Cl_4$@**1a**$_2$ was 1:1, which means the 50% of $C_2D_2Cl_4$@**1a**$_2$ was changed to $2CH_3SO_3^-$@**1a**$_2$ and accordingly the rate of the second encapsulation of $CH_3SO_3^-$ is much faster than the rate of the first encapsulation of $CH_3SO_3^-$ (see Figures S2−4 of the Supporting Information).

When the larger anion of $CH_3CH_2CO_2NBu_4$ or $(CH_3)_2CHCO_2NBu_4$ was employed under the same conditions, only one anion was encapsulated (Figure 2d). The $^{19}$F NMR spectrum of a $C_2D_2Cl_4$ solution of **1a**$_2$ and 6 equiv of $CF_3SO_3NBu_4$ showed the consistent results, two peaks at $-78.8$ ppm for free $CF_3SO_3^-$ and $-81.4$ ppm for encapsulated $CF_3SO_3^-$ in a 2:1 ratio (Figure 2e).

The negative mode ESI-MS spectrum of **1a**$_2$ and 6 equiv of $(CH_3)_2CHCO_2NBu_4$ in $C_2H_2Cl_4/CH_3CN$ showed a base peak at *m/z* 3242.34 of [$(CH_3)_2CHCO_2^-$@**1a**$_2$] showing the encapsulation of one anion per a capsule (Figure 3), whereas the same negative mode ESI-MS spectrum of **1a**$_2$ and 6 equiv of $CH_3SO_3NBu_4$ showed a base peak at *m/z* 3345.38 of [$(CH_3SO_3^- + CH_3SO_3H)$@**1a**$_2$].

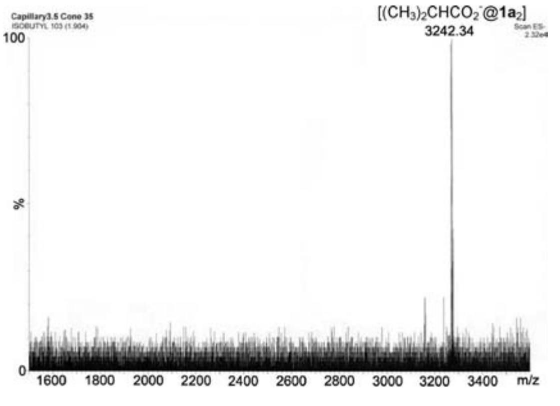

**Figure 3.** Negative-mode ESI-MS spectrum of **1a**$_2$ + 6 equiv $(CH_3)_2CHCO_2NBu_4$ in $C_2H_2Cl_4/CH_3CN$.

The formation of a capsule was confirmed by 2D NOESY spectrum of $2CH_3CO_2^-$@**1a**$_2$ in $C_2D_2Cl_4$ at 297 K. Important NOE correlations were observed between the $H_{out}$ proton of the dioxymethylene ($O-CH_{in}H_{out}-O$) at 5.86 ppm of a cavitand and the ortho-aromatic proton at 7.68 ppm (marked as a red circle in Figure 4) or the NH proton at 8.73 ppm (marked as a green circle in Figure 4) of benzoyl hydrazide groups of a counter cavitand. In the energy-minimized structure of cavitand **1a** using Spartan'04 V1.03, these protons are apart further than 5 Å. But in the energy-minimized structure for molecular capsule **1a**$_2$, the corresponding two protons are closely located at 3.78 and 2.88 Å apart, respectively, which enable the strong NOE enhancements in the NOESY spectrum. Similarly, the strong NOE correlation between the CO-NH proton at 9.71 ppm of a cavitand and the ortho-aromatic proton at 7.68 ppm of benzoyl hydrazide group (marked as a blue circle in Figure 4) of a counter cavitand is impossible without the capsular structure **1a**$_2$.

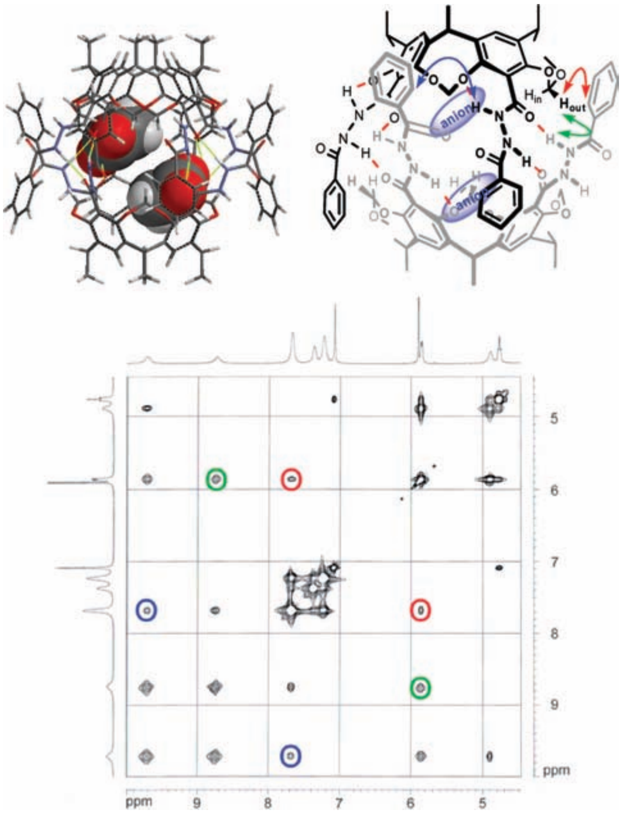

**Figure 4.** Pictorial representation of the NOE correlations of $2CH_3CO_2^-$@**1a**$_2$ in $C_2D_2Cl_4$ at 297 K ([**1a**$_2$]/[$CH_3CO_2NBu_4$] = 1/4) and the partial 2D NOESY spectrum.

The orientations of the two encapsulated acetates can be deduced from 2D NOESY spectrum wherein the NOE

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correlations were observed between the methyl protons of the encapsulated acetates and the protons of the dioxymethylene ($O-CH_{in}H_{out}-O$) as well as the *p*-hydrogen to benzoyl hydrazide group of the capsule. These results indicate that two acetate anions in the capsule **1a**$_2$ form the antiparallel pairing which locates the methyl groups into the pole of capsule and the carboxylate groups near the polar tropical region of capsule. The large upfield shift ($\Delta\delta \geq 3.72$ ppm) of the methyl protons of the encapsulated small anions are due to this antiparallel pairing which pushes the methyls deep into the pole of capsule.

To evaluate the relative stabilities of complexes, the competition experiments of guest exchange were tested. When 4 equiv of $CH_3CO_2NBu_4$ was added to the $C_2D_2Cl_4$ solution of $CH_3CH_2NH_2{\cdot}HCl$@**1a**$_2$, the resonance signal at 0.47 ppm corresponding to the methyl protons of the encapsulated ethylammonium disappeared completely and the new signal at −2.31 ppm of the encapsulated $CH_3CO_2^-$ ion appeared. But when 4 equiv of $(CH_3)_4NCl$ was added to the same solution, only the peak of free $(CH_3)_4NCl$ appeared. When a 1:1 mixture of $CH_3CO_2NBu_4$ and $CH_3SO_3NBu_4$ in $C_2D_2Cl_4$ was added to $C_2D_2Cl_4$@**1a**$_2$, only two kinds of homo complexes, $2CH_3CO_2^-$@**1a**$_2$ and $2CH_3SO_3^-$@**1a**$_2$, appeared in a 0.6:1.0 ratio (Figure 5). From these results, the stability of complex in $C_2D_2Cl_4$ depends on the encapsulated guest in the following order: $CH_3SO_3^- > CH_3CO_2^- > CH_3CH_2NH_2{\cdot}HCl \approx CH_3NH_2 \cdot HCl > (CH_3)_4N^+ >$ toluene $> C_2D_2Cl_4$. These trends were not affected by *p*-substituents of benzoylhydrazide group of **1b** and **1c**.

Presumably, the capsular stability comes from the strong ion−dipole interactions between the ionic guest and the dipoles on the equatorial−tropical areas of the capsule, which can be observed from the large chemical shifts changes of $N-H_a$ and $N-H_b$ especially when a guest with the naked charge such as $CH_3CO_2^-$ or $CH_3SO_3^-$ was complexed (two singlets at 8.4−9.8 ppm in Figure 2a or 2b vs Figure 2c or Figure 5b).

In summary, benzoyl hydrazide cavitands **1** formed the molecular capsules G@**1**$_2$ in $C_2D_2Cl_4$ stabilized by the eight intermolecular $N-H_a{\cdots}O{=}C$ hydrogen bondings, two from each four paired hydrazides, and the eight intramolecular $O-H_2C-O{\cdots}H_b-N$ hydrogen bondings, four from each two cavitands. The capsular structure, the broad spectrum of guest encapsulation phenomena, and the relative stabilities of G@**1**$_2$ were confirmed. The versatility and selectivity of encapsulation and the self-sorting properties of capsules toward guests as well as among themselves are being studied in our laboratory.

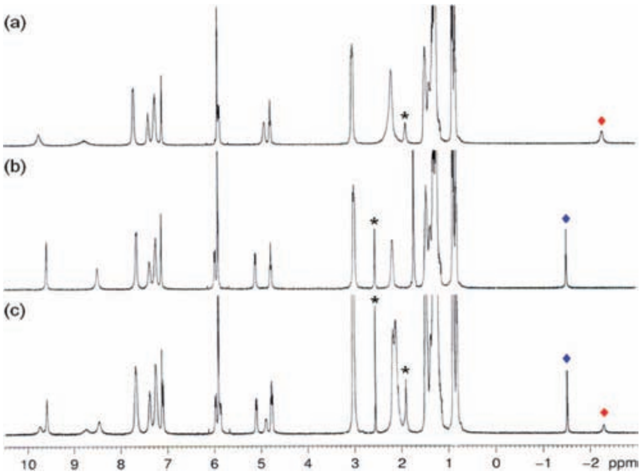

**Figure 5.** H NMR spectra (400 MHz, $C_2D_2Cl_4$, 297 K) of (a) $C_2D_2Cl_4$@**1a**$_2$ + 4 equiv of $CH_3CO_2NBu_4$, (b) $C_2D_2Cl_4$@**1a**$_2$ + 4 equiv of $CH_3SO_3NBu_4$, (c) $C_2D_2Cl_4$@**1a**$_2$ + 4 equiv of ($CH_3CO_2NBu_4$ + $CH_3SO_3NBu_4$), * = Me of free anion, red ◆, blue ◆ = Me of encapsulated anion.

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**Supporting Information Available:** Experimental details, spectroscopic data, and additional NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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