ORGANIC LETTERS

2011
Vol. 13, No. 21
5904–5907

Encapsulation of Anionic guests in a New Hydantoinylamido Molecular Capsule

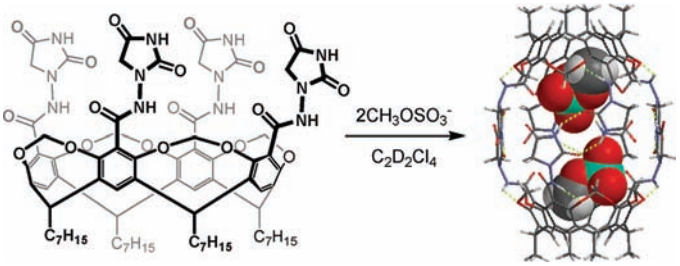
Yeon Sil Park,[†] Sungjong Seo,[†] Eun-Hee Kim,[‡] and Kyungsoo Paek*,[†]

Department of Chemistry, Soongsil University, Seoul 156-743, Korea, and Division of Magnetic Resonance, Korea Basic Science Institute, Ochang, Chungbuk 363-883, Korea

kpaek@ssu.ac.kr

Received September 21, 2011

ABSTRACT



Resorcin[4]arene-based tetrakis(*N*-hydantoinylamido)cavitand 1 forms a stable molecular capsule in the presence of suitable anionic guests such as $CH_3OSO_3^-$ or BF_4^- in $C_2D_2Cl_4$. Molecular capsule $G_2@1_2$ is stabilized by the eight intermolecular imide N-*H*···O=C hydrogen bondings, two from each four paired hydantoinyl units, and the eight intramolecular amide N-*H*···O−CH_2-O hydrogen bondings, four on each two cavitands. The formations of molecular capsules were confirmed by ^{1}H, 2D NOESY, and 2D-DOSY NMR.

Self-assembled molecular capsules[1] based on concave cavitands such as resorcin[4]arene[2] or calix[4]arenes[3] can encapsulate various types of guest molecules such as neutral, cationic, and anionic guests. The stoichiometry and the selectivity of guest encapsulation in a molecular capsule are very sensitive to the charge and steric complementarity between the guest and the capsule's inner cavity.[4]

Resorcin[4]arene-based tetramidocavitands are strong anionic receptors due to the well-organized four −(C=O)N−H···X^- hydrogen bonds upon the addition of X^-.[5] The molecular modeling study using Molecular Mechanics MMFF (PC model program: Spartan'04 V1.03) showed that a tetramidocavitand extended by hydantoin unit on the upper rim could form a new self-assembled molecular capsule through multiple hydrogen bondings, encapsulating proper anionic guests.[6] Here, the synthesis and the molecular capsule formation properties of resorcin[4]arene-based tetrakis(*N*-hydantoinylamido)cavitand **1** are reported.

[†] Soongsil University.
[‡] Korea Basic Science Institute.

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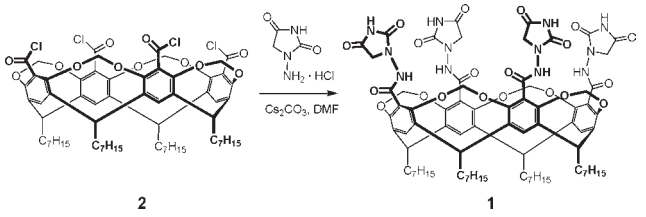
10.1021/ol202550d
Published on Web 10/11/2011

Scheme 1. Synthesis of Hydantoinylamidocavitand **1**



Tetrakis(*N*-hydantoinylamido)cavitand **1** was obtained in 74% yield from the reaction between tetrakis (chlorocarbonyl)cavitand **2**[2g] and 1-aminohydantoin hydrochloride in a mixture of Cs_2CO_3 and anhydrous DMF at room temperature (Scheme 1) followed by recrystallization from the mixtures of 20% $EtOH/CH_2Cl_2$. Cavitand **1** was fully characterized by ^1H NMR, ^{13}C NMR, high-resolution MALDI-TOF mass, and elemental analysis.

Cavitand **1** exists as a C_4-symmetric monomer in polar solvents such as DMSO or THF. The ^1H NMR spectrum in DMSO-d_6 shows well-resolved sharp proton signals, for instance, a singlet at 4.10 ppm for the $-CH_2-$ protons in the hydantoin unit (Figure 1a). The addition of various anions such as tributylmethylammonium methyl sulfate ($N(CH_3)Bu_3CH_3OSO_3$) to the DMSO-d_6 solution of cavitand **1** exhibited the peak broadening and a small downfield shifts of the imide $-NH_a$ proton in hydantoin unit, but no noticeable shift of other peaks could be observed (Figure 1b). Because the imide $-NH_a$ proton is more acidic than the amide $-NH_b$ proton, the former would be more favorable to form hydrogen-bonding with the anions.

In nonpolar solvents such as $C_2D_2Cl_4$, the ^1H NMR spectrum of cavitand **1** shows broad and uninterpretable signals due to the formation of undefinable aggregates in this solvent (Figure 1c). However, upon the addition of anionic guest such as $CH_3OSO_3^-$ to this suspension, it became a clear solution to give a well-resolved NMR spectrum (Figure 1d). A new signal of methyl proton of the complexed $CH_3OSO_3^-$ appears at -0.47 ppm ($\Delta\delta = -4.02$ ppm). Since the complexed guests are in slow exchange on the NMR time scale, the 1:1 integration ratio between cavitand **1** and anionic guest was determined easily. In the downfield region, two singlets for the imide N-*H* protons at 10.16 and amide N-*H* protons 8.60 ppm are observed, which is attributed to their hydrogen bondings. Surprisingly the peak of $-CH_2-$ protons of hydantoin unit appeared as two separated doublets ($\delta = 4.27$ and 4.08 ppm) with the typical geminal coupling constants ($^2J = 16$ Hz). These results may be due to the guest-assisted dimeric molecular capsule formation, $2CH_3OSO_3^-@\mathbf{1}_2$, in $C_2D_2Cl_4$, which made the $-CH_2-$ protons in a hydantoin unit diastereotopic due to the restricted free rotation of N–N single bond by intermolecular imide N-$H\cdots$O=C hydrogen bondings as shown in Figure 1.

When $CH_3OSO_3^-$ was added to cavitand **1** in 10% $CD_3OD/C_2D_2Cl_4$, ^1H NMR spectrum showed a singlet at 4.15 ppm for enantiotopic $-CH_2-$ protons in the hydantoin unit, and the methyl protons of complexed $CH_3OSO_3^-$ appears at -0.51 ppm ($\Delta\delta = -3.75$ ppm) (Figure 1e). These chemical shift changes signify the dissociation of capsular complex to monomeric complex (caviplex), $CH_3OSO_3^-@\mathbf{1}$, due to the competitive hydrogen-bonding ability of CD_3OD. The same 1:1 complexation was observed for a large anionic guest such as $CH_3CH_2CH_2SO_3^-$ (Figure 1f).

Dimeric capsular complexation was also observed for BF_4^-. In the downfield region of Figure 1g, the peak of imide N-*H* protons is observed in the same position (10.16 ppm) with that of $2CH_3OSO_3^-@\mathbf{1}_2$ in Figure 1d, which implies the same intermolecular imide -N*H*$\cdots$O=C hydrogen bonding. But the peaks of amide $-NH_b$ protons appeared at 7.80 and 8.60 ppm, respectively, which are due to the difference of

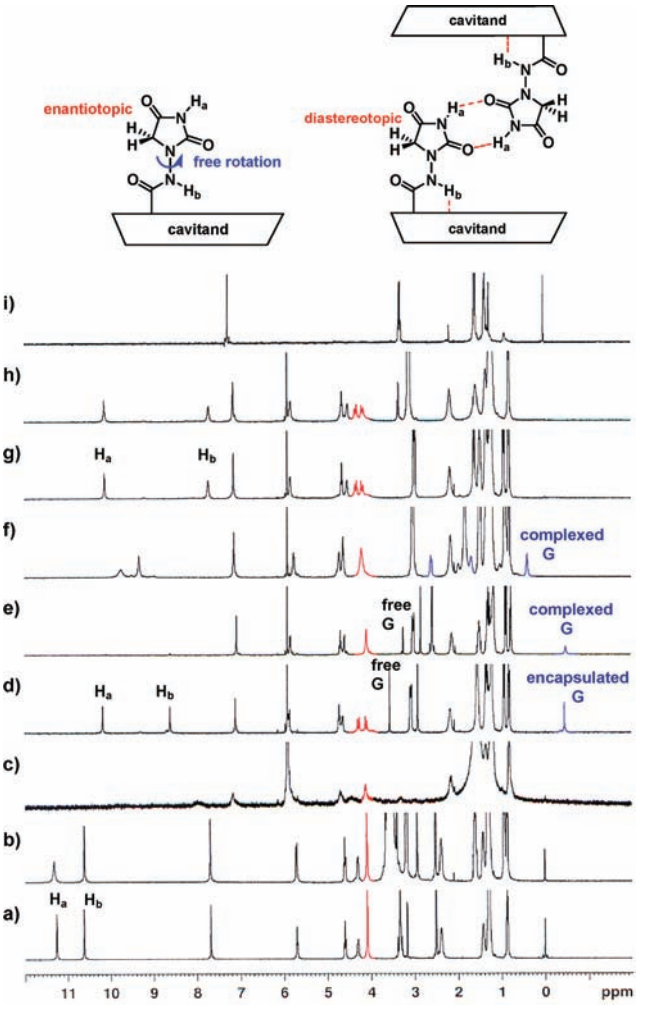


Figure 1. Schematic representation of hydrogen bonds in cavitand **1** and the ^1H NMR (400 MHz, 298 K) spectra: (a) **1** in DMSO-d_6, (b) **1** + $CH_3OSO_3^-$ in DMSO-d_6, (c) **1** in $C_2D_2Cl_4$, (d) **1** + $CH_3OSO_3^-$ in $C_2D_2Cl_4$, (e) **1** + $CH_3OSO_3^-$ in 10% $CD_3OD/C_2D_2Cl_4$, (f) **1** + $CH_3CH_2CH_2SO_3^-$ in $C_2D_2Cl_4$, (g) **1** + $BF_4^-(NBu_4^+)$ in $C_2D_2Cl_4$, (h) **1** + $BF_4^-(NEt_4^+)$ in $C_2D_2Cl_4$, (i) **1** + $BF_4^-(NEt_4^+)$ in $CDCl_3$. ($[\mathbf{1}]_{total} = 4$ mM, $[G]_{total} = 6$ mM.)

hydrogen bonding energies of BF_4^- and $CH_3OSO_3^-$ with amide $-NH_b$.

It was also observed that the cooperative binding of anion and solvent can play an important role in the formation of molecular capsule. In the case of NBu_4BF_4 (Figure 1g) or NEt_4BF_4 (Figure 1h) in $C_2D_2Cl_4$, the diastereotopic $-CH_2-$ protons in hydantoin unit were detected, but in $CDCl_3$ cavitand **1** was insoluble (Figure 1i). This implies that cavitand **1** with BF_4^- in $C_2D_2Cl_4$ exists as dimeric molecular capsular complex of $BF_4^-\cdot C_2D_2Cl_4\cdot BF_4^-@\mathbf{1}_2$ to fill the capsular cavity complementarily.

Overall the formation of capsule is strongly dependent on guest and solvent. In case of carboxylate, PF_6^-, halogen anions, or other anions except $CH_3OSO_3^-$ and BF_4^-, no dimeric capsular complex was observed in the various conditions.

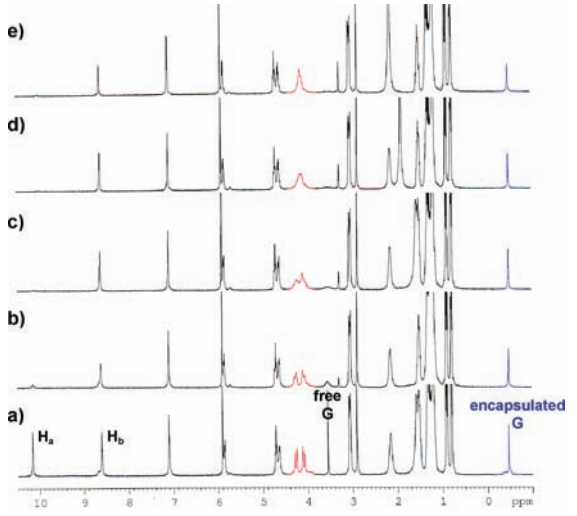


Figure 2. ^{1}H NMR (400 MHz, 298 K, $C_2D_2Cl_4$) spectra showing the changes of topicity of $-CH_2-$ hydantoin unit in dimeric complex, $2CH_3OSO_3^-@\mathbf{1}_2$ by the addition of CD_3OD: (a) 0 μL, (b) 10 μL, (c) 20 μL, (d) 30 μL, (e) 40 μL. ($[\mathbf{1}]_{total}$ = 4 mM, $[CH_3OSO_3^-]_{total}$ = 6 mM.)

To confirm the formation of dimeric capsular complex ($2CH_3OSO_3^-@\mathbf{1}_2$), a titration experiment with CD_3OD was performed (Figure 2). CD_3OD was titrated into a solution of $2CH_3OSO_3^-@\mathbf{1}_2$ in $C_2D_2Cl_4$ (500 μL) with 10 μL increments until the solution contained ~20 vol % CD_3OD. The capsule dissociation could be followed by the change of topicities of $-CH_2-$ hydantoin unit in ^{1}H NMR spectrum. In the presence of ~6 vol % of CD_3OD (Figure 2d), most dimeric capsules dissociated to caviplex. The imide $-NH$ protons at 10.16 ppm broadened and disappeared rapidly by deuterium exchanges with CD_3OD. But the intensity of the amide $-NH$ protons at 8.60 ppm was gradually reduced, which is attributed to the stable hydrogen bonding of amide $-NH\cdots$anion. The intensity of the complexed guests slowly decreased, which implies that caviplex $CH_3OSO_3^-@\mathbf{1}$ is also comparatively stable in the given conditions.

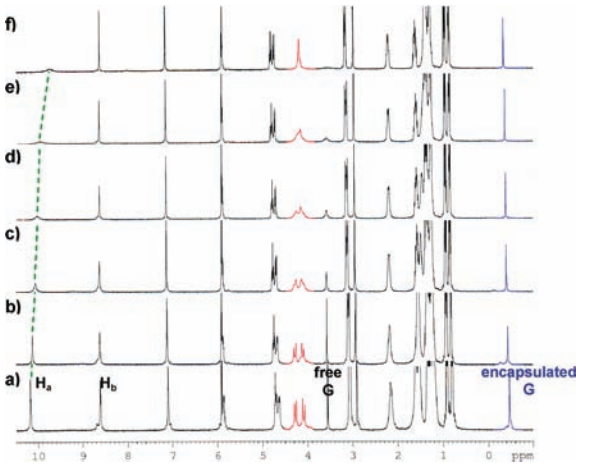


Figure 3. ^{1}H NMR (400 MHz, $C_2D_2Cl_4$) spectra showing the changes of topicity of $-CH_2-$ hydantoin unit in dimeric complex, $2CH_3OSO_3^-@\mathbf{1}_2$ at variable temperature: (a) 25 °C, (b) 40 °C, (c) 60 °C, (d) 70 °C, (e) 80 °C, (f) 90 °C. ($[\mathbf{1}]_{total}$ = 4 mM, $[CH_3OSO_3^-]_{total}$ = 6 mM.)

The temperature dependencies of hydrogen bonding interactions for $2CH_3OSO_3^-@\mathbf{1}_2$ were also observed (Figure 3). As the temperature rises, the peak of H_a shifts to high field and the diastereotopic CH_2 peak at 4.18 ppm becomes enantiotopic, which means the dissociation of capsular complex to caviplex increases. When the temperature exceeds 70 °C, the most $-CH_2-$ protons in hydantoin unit became enantiopic, which implies mostly caviplex $CH_3OSO_3^-@\mathbf{1}$ exists.

The formation of molecular capsule was also confirmed by 2D NOESY spectrum of $2CH_3OSO_3^-@\mathbf{1}_2$ in $C_2D_2Cl_4$ at 297 K.

Important NOE correlations were observed between the imide $-NH_a$ proton at 10.16 ppm of a cavitand and outer proton (H_{out}) of the dioxymethylene bridge ($O-CH_{in}-H_{out}-O$) at 5.86 ppm or inner protons proton (H_{in}) at 4.63 ppm of a counter cavitand (marked as a red circle in Figure 4). In the energy-minimized structure of cavitand **1** using Spartan'04 V1.03, these protons are apart further than 6 Å. But in the energy-minimized structure for molecular capsule $\mathbf{1}_2$, the corresponding two protons are closely located at 3.0 Å and 4.1 Å apart, respectively, which enables the strong NOE enhancements in the NOESY spectrum. Similarly, the strong NOE correlation between the imide $-NH_a$ proton at 10.16 ppm of a cavitand and the amide $-NH_b$ proton at 8.60 ppm of a counter cavitand (marked as a blue circle in Figure 4) is also possible only in a capsular structure $\mathbf{1}_2$.

For the methyl signal of encapsulated $CH_3OSO_3^-$ at −0.47 ppm, its NOE correlations with all the protons of cavitand **1** except those of alkyl feet and H_a are observed, indicating that two $CH_3OSO_3^-$ exists as the antiparallel pairing which pushes the methyls deep into the pole of capsule.

The formation of molecular capsular complex, $2CH_3OSO_3^-@\mathbf{1}_2$, was also confirmed by diffusion coefficient

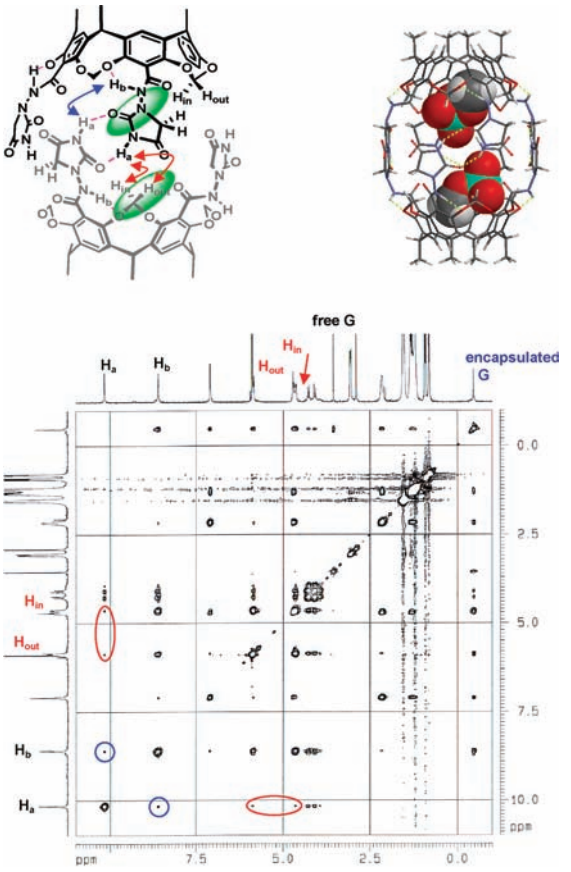


Figure 4. Pictorial representation of the NOE correlation of $2CH_3OSO_3^-@\mathbf{1}_2$ in $C_2D_2Cl_4$ at 298 K and the 2D-NOESY spectrum (400 MHz). ($[\mathbf{1}]_{total}$ = 4 mM, $[CH_3OSO_3^-]_{total}$ = 6 mM.)

measurements using a 2D-DOSY NMR technique in $C_2D_2Cl_4$ at room temperature (Figure 5). All the peaks including the encapsulated anions have the same diffusion coefficients (D values) within experimental errors (1.66×10^{-10} m^2 s^{-1}). These results clearly mean that hydantoinylamidocavitand **1** and $CH_3OSO_3^-$ exist as a single supramolecular entity in solution.

To demonstrate encapsulation of two molecules of anion in a capsule, the same 2D DOSY experiments in 6 vol% of $CD_3OD/C_2D_2Cl_4$ were performed. The addition of only 6 vol % of CD_3OD dissociates capsule $2CH_3OSO_3^-@\mathbf{1}_2$ into caviplex $CH_3OSO_3^-@\mathbf{1}$. Caviplex $CH_3OSO_3^-@\mathbf{1}$ is half molecular weight and size of capsule $2CH_3OSO_3^-@\mathbf{1}_2$. As expected, the diffusion coefficient (2.45×10^{-10} m^2 s^{-1}) of caviplex $CH_3OSO_3^-@\mathbf{1}$ was larger than that of capsule $2CH_3OSO_3^-@\mathbf{1}_2$ (1.66×10^{-10} m^2 s^{-1}), which confirms that cavitand **1** forms molecular capsular complex $2CH_3OSO_3^-@\mathbf{1}_2$ in $C_2D_2Cl_4$ solution.[7]

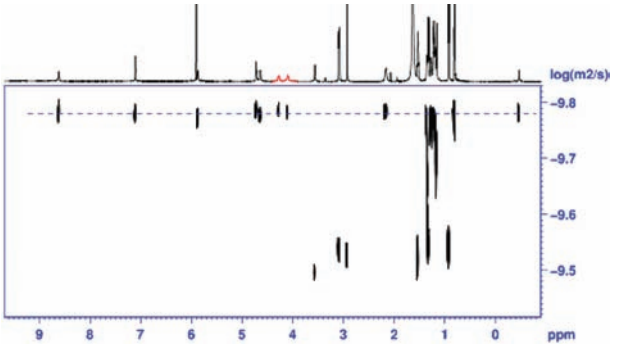


Figure 5. 2D-DOSY NMR (900 MHz) spectrum of $2CH_3OSO_3^-@\mathbf{1}_2$ in $C_2D_2Cl_4$ at 298 K. ($[\mathbf{1}]_{total}$ = 4 mM, $[CH_3OSO_3^-]_{total}$ = 6 mM.)

In conclusion, tetrakis(*N*-hydantoinylamido)cavitand **1** self-assembled with the complementary anionic guests such as $CH_3OSO_3^-$ or BF_4^- in $C_2D_2Cl_4$ to give molecular capsule $2CH_3OSO_3^-@\mathbf{1}_2$ or $BF_4^-\cdot C_2D_2Cl_4\cdot\cdot BF_4^-@\mathbf{1}_2$, which was confirmed by solvent titration, VT ^1H NMR, 2D-NOESY, and 2D-DOSY NMR experiments. Molecular capsule $2CH_3OSO_3^-@\mathbf{1}_2$ is stabilized by the eight intermolecular imide N-$H\cdots$O=C hydrogen bonds, two from each of four paired hydantoinyl units, and the eight intramolecular amide N$-H\cdots$O$-$CH$_2-$O hydrogen bonds, four on each two cavitands. The formation of molecular capsule is strongly dependent on guests and solvents.

Acknowledgment. This work was supported by CBMH (Yonsei University) and the Korea Research Foundation Grant funded by the Korean Government (KRF-2009-0072919).

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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