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Encapsulation of Small Organic Molecules by a Self-Assembled Molecular Capsule through Charged Hydrogen Bonding Interaction

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Abstract: Self-assembled heterodimeric molecular capsule based on the charged hydrogen bonding interaction between two different CTV monomers (**1** and **2**) was developed. The formation of the molecular capsule was confirmed by inclusion phenomena of complementary neutral guests in DMSO-d_6. The encapsulated TMS was released by prolonged heating or pH adjustment. Molecular modeling and intermolecular NOEs suggested the three-dimensional structure of the termolecular inclusion complex. Copyright © 1996 Elsevier Science Ltd

Supramolecular structures such as enzyme complexes, ribosomes, protein filaments, viruses, and membranes are not made as single, giant, covalently linked molecules; instead they are formed by the noncovalent assembly of preformed macromolecular subunits.[1] Some outstanding examples of biological self-assembling molecular structures are the rodlike and filamentous viruses, in which the helical aggregation of the protein-coat subunits forms a cylindrical container for the virus's nucleic acid.[2] Recently, noncovalent self-assembly process used in the biological organization has been increasingly exploited in the design of synthetic receptors.[3] Herein, we describe a molecular assembly technique for constructing three-dimensional molecular capsule[4] based on the charged hydrogen bonding interaction (electrostatic interaction) between two different cyclotriveratrylene (CTV)[5] derivatives.

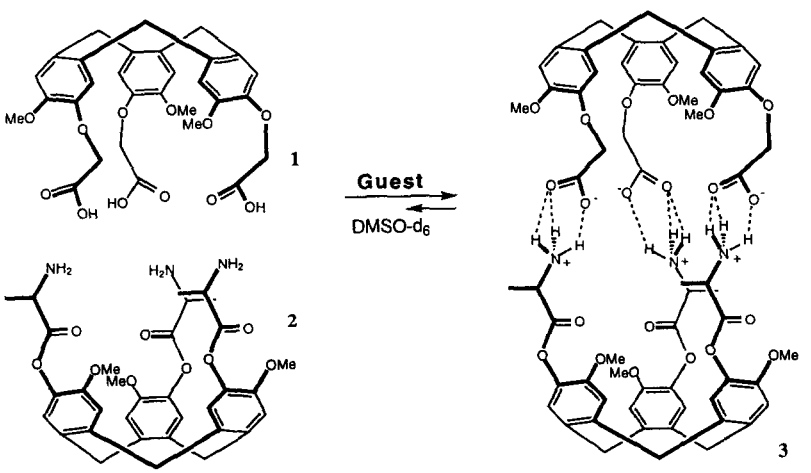

Figure 1. Self-Assembly based on the charged hydrogen bonding interaction between CTV trisacid (**1**) and CTV trisamine (**2**).

Since bowl-shaped C_3-symmetric CTV monomers[6] can have functional groups on the upper rim that would recognize each other, CTV heterodimer assembled noncovalently from two different CTV monomers should result in a molecular capsule which can encapsulate suitable molecules of complementary size and shape. As shown in Figure 1, we designed a self-assembled molecular capsule based on the charged hydrogen bonding interactions between carboxylates on one CTV monomer (**1**) and ammoniums on the complementary CTV monomer (**2**).[7]

Each CTV trisacid (**1**) and trisamine (**2**) is soluble in acetone. However, the mixture of **1** and **2** is not soluble in almost all the organic solvent except DMSO. The NMR spectrum of 1:1 mixture of **1** and **2** at less than 1 mM concentration in DMSO-d_6 shows the simple combination of each unaffected spectrum of **1** and **2**, indicating formation of the potential dimeric structure.[8] In fact, the formation of a self-assembled molecular capsule was confirmed by inclusion phenomena of neutral guests at less than 1mM concentration in DMSO-d_6. Exchange of all guests in and out of the cavity is very slow at rt on the NMR time scale. The inclusion phenomena were elucidated by upfield shifts of included guest signal (see Table 1) because of its location in the shielding region of the aromatic cavity. To **1** dissolved in acetone was added 1% TMS in acetone and then **2** in acetone. Then solid immediately formed out of acetone. After removing acetone in *vacuo*, the NMR spectrum was taken in deuterated DMSO. In comparison with 1:0.4 and 1:0.6 mixture of **1** and **2**, 1:1 mixture is capable of capturing more TMS inside the cavity of the capsule, indicating the capsule formation by self-assembly.

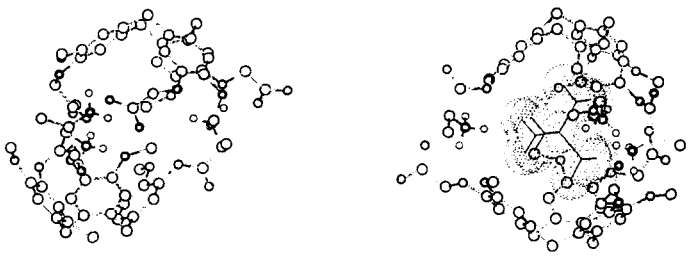

Figure 2. Energy-minimized structures of the vacant CTV heterodimer (left) and the TMS-occupied CTV heterodimer (right) (DISCOVER 95.0 with CVFF force field).[9]

Computer-generated structure of the vacant CTV heterodimeric assembly is compared with that of the inclusion complex of CTV heterodimer and TMS (Figure 2). Upon inclusion of TMS, the originally distorted unsymmetrical heterodimeric structure is reorganized around TMS to make maximum van der Waals contacts with the encapsulated TMS and form a spherical capsule.[9]

Since the hydrogen bonding interaction between carboxylate and ammonium is expected to be very strong, the rigidity of the CTV heterodimeric assembly was tested by release of the encapsulated TMS upon heating at 60 °C in the sealed nmr tube. With prolonged heating, the amount of released TMS increases. However, even after 2 weeks, less than 50% of TMS is released showing the rigidity of the capsule.[10]

Addition of trifluoroacetic acid to CTV heterodimer•TMS complex regenerated **1**, **2**, and free TMS. This demonstrates that formation of the complex is not completely irreversible and rather it can be switched by pH adjustment.[4e]

In order to elucidate three-dimensional structure of the termolecular complex, we performed intermolecular NOE study of CTV heterodimer and TMS complex. Irradiation of the methyl protons of the encapsulated TMS caused sizable increases in signal strengh in 5 different kinds of protons of CTV heterodimer. (Figure 3) In

fact, strong NOEs between TMS methyl protons and methoxy protons and methyl protons in alanine side chain indicates that both methoxy groups and methyl side chains in CTV heterodimer are pointing toward the cavity and therefore makes a good hydrophobic environment for encapsulating the neutral guest.

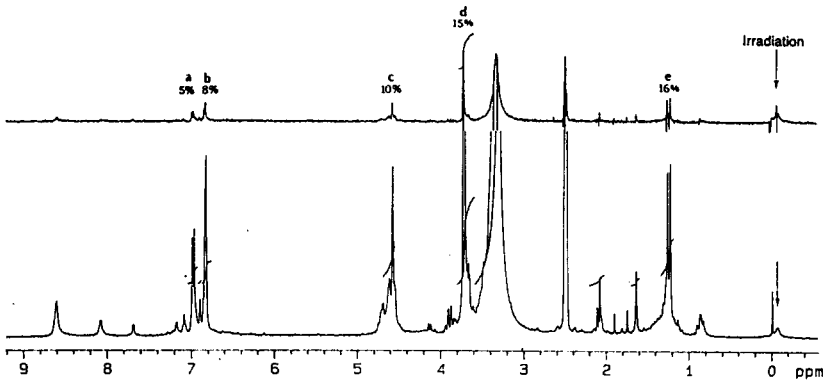

Figure 3. NOE difference spectrum of CTV heterodimer•TMS complex (top) and 500 MHz ^{1}H NMR spectrum of CTV heterodimer•TMS complex in DMSO-d_6 (bottom). The signals around 2.5 and 2.1 ppm are from the solvents (DMSO-d_6 and acetone) and the signals around 1.6 and 0.8 ppm from impurities. The large signal around 3.3 ppm is from residual water. The signal at 0 ppm corresponds to free TMS. The arrow indicates irradiation of the included TMS protons. Peaks labeled "a~e" are intermolecular NOEs (a; Ar*H* of **1**, b; Ar*H* of **2**, c; Ar-OCH_2-COOH of **1**, d; Ar-OCH_3 of **1** and **2**, e; alanine CH_3 of **2**).

Table 1 shows relative stabilities (K_{rel}) of the termolecular complexes between CTV heterodimer and guests. The inclusion constant (K_{inc}) was determined by integrating the bound guest signal in the NMR spectra of 1:1 mixture of **1**, **2**, and the same amount of guest in DMSO-d_6. The inclusion constant (K_{inc}) is roughly correlated with guest volume except bromoform, indicating that van der Waals interaction is operative in the guest inclusion. However, since the molecular modeling indicates that the cavity can accomodate all the guest used,[11] the difference in the relative stabilities seems to depend not only on the van der Waals contacts with the concave inner surface, but also presumably on the solvation effect.[12]

Table 1. Inclusion of guest molecules in the cavity of the CTV heterodimer.

Guest	K_{inc} (K_{rel})[a]	$\Delta\delta$ (ppm)[b]	Guest vol.(Å^3)[c]
tetramethylsilane	40 (200)	0.07	107
t-butyl chloride	6 (30)	0.21	96
1,1,1-trichloroethane	5 (25)	0.44	89
chloroform	3 (15)	3.20	69
bromoform	0.2 (1)	1.95	93

a.Inclusion constant (K_{inc}, M^{-1}) at 293 K. K_{inc} = [**1**•G•**2**]/[**1**•**2**][G], where **1**•**2** is CTV heterodimer and **1**•G•**2** is **3**•guest termolecular complex. b.Upfield shift of the included guest signal. c. The guest volume was calculated according to ref.13.

In conclusion, we developed a self-assembled heterodimeric molecular capsule based on the charged hydrogen bonding interaction between two different CTV monomers (**1** and **2**). The formation of the molecular capsule was confirmed by almost irreversible inclusion phenomena of complementary neutral organic molecules

in DMSO-d_6, as evidenced by NMR spectroscopy. Release of the encapsulated TMS can be controlled by prolonged heating or pH adjustment. Computational molecular modeling and intermolecular NOEs suggested the three-dimensional structure of the termolecular inclusion complex. Since the charged hydrogen bonding interaction is so strong even in DMSO which is a strong hydrogen bonding acceptor and strongly precludes the formation of hydrogen bond based complex, we plan to attach water-soluble group to each CTV to achieve reversible encapsulation of suitable guest molecules of complementary shape and size in hydroxylic solvents such as methanol or water-containing solvent.

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6. Spectral data for **1**: mp 167 ~ 170 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.99 (s, 3 H, Ar*H*), 6.97 (s, 3 H, Ar*H*), 4.66 (d, *J* = 13.5 Hz, 3 H, Ar-CH$_{in}$*H*$_{out}$-Ar), 4.61 (s, 6 H, Ar-OC*H*$_2$-), 3.72 (s, 9 H, Ar-OC*H*$_3$), 3.46 (d, *J* = 13.5 Hz, 3 H, Ar-C*H*$_{in}$H$_{out}$-Ar); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 170.3, 147.4, 145.6, 132.7, 131.5, 115.0, 113.8, 65.2, 55.7, 35.0.; IR (KBr) 3340, 2960, 2912, 1734, 1603, 1507, 1328, 1257, 1139, 1083, 998, 934, 889 cm^{-1}.; MS (FAB) m/z 582 (M$^+$). **2**: mp 155 ~ 160 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.83 (s, 3 H, Ar*H*), 6.81 (s, 3 H, Ar*H*), 4.57 (d, *J* = 13.5 Hz, 3 H, Ar-CH$_{in}$*H*$_{out}$-Ar), 3.88 (q, *J* = 7.5 Hz, 3 H, C*H*CH$_3$), 3.71 (s, 9 H, Ar-OC*H*$_3$), 3.35 (d, *J* = 13.5 Hz, 3 H, Ar-C*H*$_{in}$H$_{out}$-Ar), 1.25 (d, *J* = 7.0 Hz, 9 H, CHC*H*$_3$); ^{13}C NMR (50.3 MHz,CDCl$_3$) δ 174.9, 149.5, 138.3, 137.8, 131.3, 123.6, 114.0, 56.2, 50.1, 36.4, 20.6.; MS (FAB) m/z 622 (M$^+$+1).
7. Since **1** and **2** exist in enantiomer pairs, there are two ways of self-assembly. The first one in Figure 1 is derived from the same CTV's. The second way of assembly is derived from two different enantiomeric CTV's.
8. NMR spectrum of 1:1 mixture of **1** and **2** at 7 mM concentration in DMSO-d_6 indicates formation of the oligomeric structure, indicating that formation of the dimeric or oligomeric structure from 1:1 mixture of **1** and **2** is concentration-dependent.
9. The energy-minimized structures were obtained with DISCOVER 95.0 of MSI on a Silicon Graphics INDY workstation.
10. In comparison with release rate, inclusion rate of outide TMS into the cavity of the preformed capsule upon heating also turned out to be very slow.
11. The cavity volume of the TMS-occupied CTV heterodimer (calculated from the average radius of the pseudo-spherical cavity, considering the van der Waal's half-thickness of the aromatic rings (1.77 Å)), which is the largest among those examined, is ~150 Å^3 which is ~40% larger than TMS.
12. Data of the solvation energy for guest dissolved in DMSO-d_6 are not available.
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