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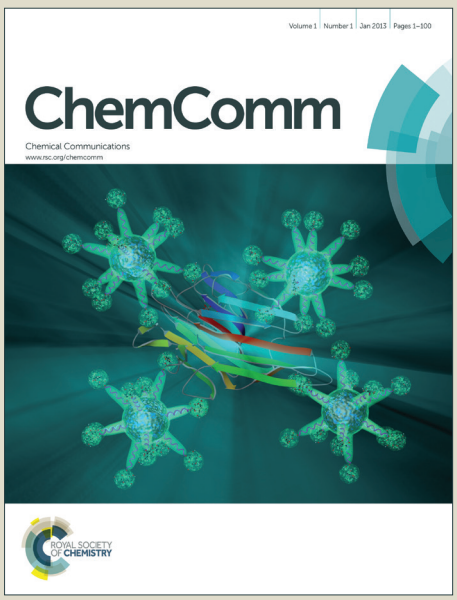

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A chromogenic molecular capsule attributable to dipolar amide resonance structure

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A new chromogenic, self-assembled molecular capsule G@2_2 is developed by introducing four (*N*,*N*-dimethyl-4-aminophenyl) azobenzyl moieties on the upper rim of a resorcin[4]arene-based amidoimino-cavitand. The tuning of conjugation between amido and (*N*,*N*-dimethyl-4-aminophenyl)azobenzyl groups by acid-base titration allows naked-eye detection of molecular capsule formation.

Interests in developing new self-assembled molecular capsules have been unabated for more than a decade. In the presence of suitable guest molecules self-assembled molecular capsules are spontaneously formed in solution by multiple hydrogen bonds,[1] metal-ligand interactions,[2] hydrophobic interactions,[3] and hybrid noncovalent interactions.[4] The characteristics of their nano-sized cavities as molecular receptor, sensor, reactor, storage, and delivery systems are widely reported.[5]

Although various molecular capsules with distinctive properties are well-studied, 'naked eye' detection of monomer-to-dimeric capsule and vice versa is not reported yet due to the difficulty in designing a sensitive capsular chromogenic system.

N,N-Disubstituted azobenzene dyes exist in acidic solution as an equilibrium mixture of two tautomers - ammonium form **A** (yellow) and quinoid form **B** (reddish purple).[6] (Fig. 2(a)) The ammonium form **A** is favorable in high pH, but the tautomeric equilibrium gradually shifts to favor **B** as pH decreases.[7] This tautomeric equilibrium in acidic solution was confirmed by Raman spectra[8(a)-(b)] as well as ^{15}N and ^{13}C NMR[8(c)].

Amide group exists as two resonance structures[9] - neutral structure **C** and dipolar structure **D**, and neutral structure **C** is favourable than dipolar structures in neutral pH. For instance, Kemnitz *et al*. reported that the relative concentrations of neutral structure **C** and dipolar structure **D** in acetamide are 60% and 25%, respectively.[9(b)] When an amide group hydrogen bonds, the dipolar structure **D** becomes favorable.[10]

If a protonated *N,N*-disubstituted azobenzene dye combines with an amide group, dipolar resonance structure **D** could extend its conjugation up to the protonated *N,N*-disubstituted azobenzene dye (Fig. 1(c) tautomer **E**).

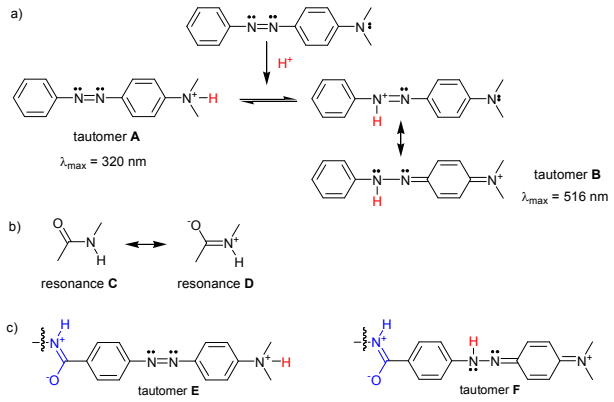


Fig. 1 a) Two tautomers (**A** and **B**) of *N,N*-disubstituted azobenzene dye, b) two resonance structures (**C** and **D**) of amide group, c) tautomers **E** and **F**: the combinations of tautomer **A** or **B** and resonance structure **D**.

We have recently demonstrated that imino-cavitand **1** containing four benzamido moieties on its upper rim efficiently self-assembles into thermally inert molecular capsule **G@1**$_2$ in the presence of complimentary guests such as toluene or 1,4-dimethoxy benzene via eight intermolecular amide N–H···O=C hydrogen bonds. (Fig. 1(a))[1(k)]

When a *N,N*-disubstituted azobenzene dye is coupled to cavitand **1**, the extent of conjugation between amide group and a *N,N*-disubstituted azobenzene dye (tautomer **E**) may depend on the stable hydrogen bond of amide group and acid concentration. In this paper,

we report the first naked-eye detection of the assembly and disassembly of a chromogenic, self-assembled molecular capsule.

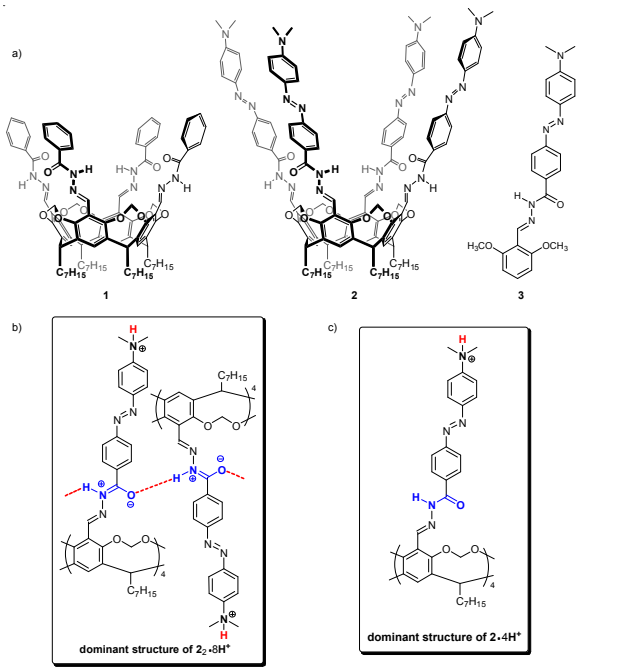
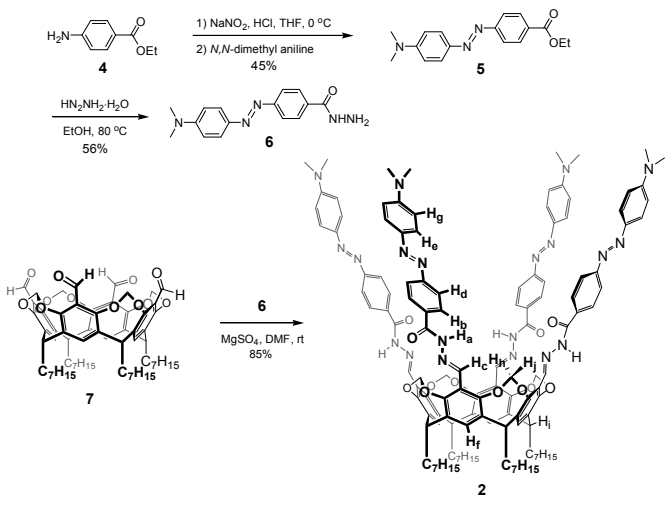


Fig. 2 a) Benzamido-iminocavitand **1** and **2** for self-assembled molecular capsule, and model compound **3** b) suggested structures of chromogenic molecular capsule $\mathbf{2}_2 \cdot 8H^+$, c) protonated cavitand $\mathbf{2} \cdot 4H^+$.



Scheme 1. Synthesis of cavitand **2**.

In order to introduce azobenzene moiety on the upper rim of iminocavitand **1**, diazo-benzoic hydrazide derivative **6** was synthesized in two steps from ethyl 4-aminobenzoate **4**. The diazonium salt obtained from the reaction of ethyl 4-aminobenzoate **4** with $NaNO_2$ in the presence of HCl at 0 °C was in situ added to a THF solution of *N*,*N*-dimethyl aniline to give diazo-compound **5** as a red solid in 45% yield. Diazo-benzoic hydrazide **6** was prepared in 56% yield from the reaction of **5** with excess hydrazine. C_4-symmetric iminocavitand **2** was obtained in 85% yield from the condensation reaction between tetraformyl cavitand **7**[11] and hydrazide **6** in a mixture of $MgSO_4$ and dry DMF at room temperature. The structure of cavitand **2** was fully characterized by ^{1}H NMR, ^{13}C-NMR spectroscopy, high-resolution MALDI-TOF mass spectrometry, and elemental analysis.

Cavitand **2** forms a stable molecular capsule, toluene-d_8@$\mathbf{2}_2$, in toluene-d_8, whose structure was confirmed using ^{1}H NMR and 2D-NOESY experiments (Fig. S3, ESI).

To examine whether hydrogen-bond-induced dipolar amide (resonance structure **D**) forms a significant electronical conjugation with protonated *N*,*N*-dimethylamino group as shown Fig. 2 (b), UV-Vis absorption shift of molecular capsule toluene@$\mathbf{2}_2$ was investigated through CH_3SO_3H titration in toluene (Fig. 3).

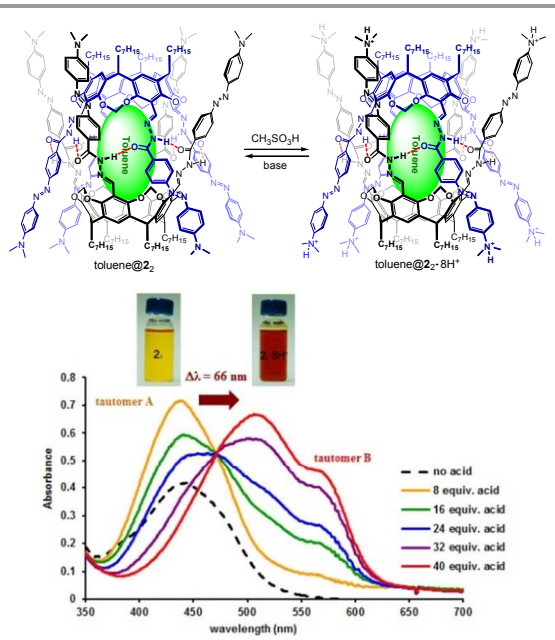


Fig. 3 Changes in UV-Vis absorption spectra of toluene@$\mathbf{2}_2$ (4.7×10^{-6} M in toluene) upon addition of CH_3SO_3H.

Upon addition of 8.0 equiv. of CH_3SO_3H, the protonated capsule toluene@$\mathbf{2}_2 \cdot 8H^+$ shows a distinct hyperchromic effect with 1.7-fold enhancement of ε at λ_{max} = 440 nm compared to that of capsule toluene@$\mathbf{2}_2$ (yellow solution). As more acid was added up to 40.0 equiv., this band (λ_{max} = 440 nm) shifted to 506 nm ($\Delta\lambda$ = 66 nm) with isosbestic point at 471 nm (red solution). Also a band at λ_{max} = 564 nm (from quinoid tautomer **F**) increased gradually. This process can be reversed by addition of organic bases such as pyridine, triethylamine, and DBU. These phenomena indicate that the strong intermolecular hydrogen-bond-induced dipolar amide resonance of molecular capsule toluene@$\mathbf{2}_2 \cdot 8H^+$ (Fig. 2(b)) becomes more predominant upon addition of acid. And the heavily extended conjugation explains the color change as well as hyperchromic effect.

In order to prove that the strong hydrogen bond-assisted dipolar amide resonance structure **D** as shown Fig. 2 (b) is important for the bathochromic shift, acid titration experiments of cavitand **2** and model compound **3** were performed (Fig. 4). Cavitand **2** in 8% methanol/toluene cannot form molecular capsule (Fig. 6(c)) and neutral amide resonance **C** is favorable in this condition (Fig. 2(c)). When CH_3SO_3H was added to a solution of cavitand **2** in 8% methanol/toluene, no bathochromic shift was observed. Only slight equilibrium shift to quinoid tautomer **B** was gradually observed as the acid concentration increased (Fig. 4(a)). Similar result was observed for model compound **3** in toluene (1.4×10^{-4} M) (Fig. 4(b)).

These tautomeric equilibrium shift is characteristic for *N,N*-disubstituted azobenzene dyes in acidic solution.[6-8]

These results prove that strong hydrogen bond-assisted dipolar amide group of molecular capsule toluene@$\mathbf{2}_2$·8H$^+$ (Fig. 2(b)) is the key to its chromogenic phenomena.

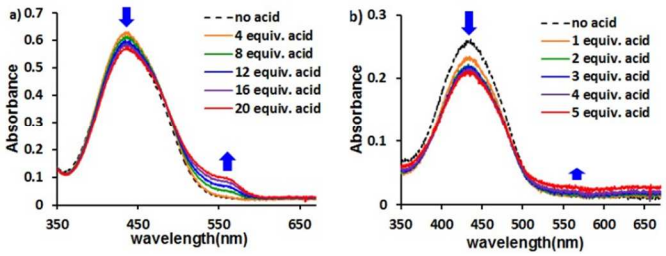


Fig. 4 a) Changes in UV-Vis absorption spectra upon addition of CH_3SO_3H: a) cavitand **2** (4.7×10^{-6} M in 8% methanol/toluene), b) model compound **3** (1.4×10^{-4} M in toluene).

Fig. 5 shows the UV-Vis absorption shift of the protonated molecular capsule, toluene@$\mathbf{2}_2$·8H$^+$ by addition of methanol. As methanol increases, the band with λ_{max} = 506 nm disappears and a new blue-shifted ($\Delta\lambda$ = -72nm) absorption band with λ_{max} = 434 nm appears with isosbestic point at 458 nm. This blue shift implies that the protonated molecular capsule, toluene@$\mathbf{2}_2$·8H$^+$ dissociates to cavitand **2**·4H$^+$ upon methanol addition, losing electrical conjugation. As a result, the red color of molecular capsule, $\mathbf{2}_2$·8H$^+$ turned yellow.

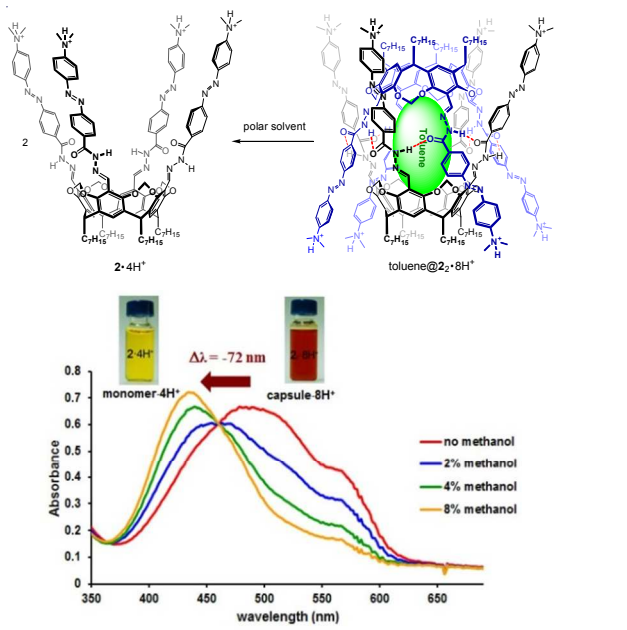


Fig. 5 Changes in UV-Vis absorption spectra of toluene@$\mathbf{2}_2$·8H$^+$ (4.7×10^{-6} M in toluene) upon addition of methanol.

The conversion from capsule to cavitand was also observed in ^{1}H NMR. ^{1}H NMR spectrum of molecular capsule $\mathbf{2}_2$·8H$^+$ in toluene-d_8 shows sharp and highly symmetrical proton signals (Fig. 6(a)). The intermolecular hydrogen-bonding amide N-*H* protons of molecular capsule appear as a singlet at 12.74 ppm, and the signals of inner (H_h) and outer (H_j) protons of the dioxymethylene bridge and methine protons (H_i) appear at 4.35, 6.40, and 4.88 ppm as a pair of doublets and a triplet, respectively. And the methyl protons of heptyl feet are observed at 0.84 ppm as a triplet. Adding CD_3OD to the this molecular capsule solution broke intermolecular amide N–H···O=C hydrogen bonds due to the competitive hydrogen-bonding ability of CD_3OD, and the conversion from molecular capsule to cavitand can be observed by ^{1}H NMR spectrum. The ^{1}H NMR spectrum in the presence of 2% CD_3OD (Fig. 6(b)) showed both signals of dimeric capsule $\mathbf{2}_2$·8H$^+$ (**black**) and dissociated cavitand **2**·4H$^+$ (**green**). Capsule $\mathbf{2}_2$·8H$^+$ and cavitand **2**·4H$^+$ exist as an equilibrium mixture in a 62:38 ratio, which is inferred from comparing ^{1}H NMR integration ratios.

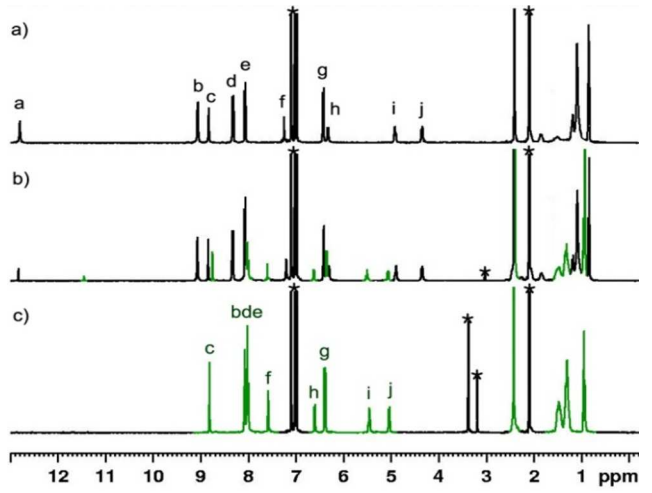


Fig. 6 ^{1}H NMR spectra (400 MHz) in toluene-d_8 at 298 K of: a) toluene-d_8@$\mathbf{2}_2$·8H$^+$ b) after the addition of 2% CD_3OD, c) after the addition of 8% CD_3OD. [$\mathbf{2}_2$] = 5 mM. The signals of capsule $\mathbf{2}_2$·8H$^+$ (**black**) and cavitand **2**·4H$^+$ (**green**) are highlighted. The residual peaks of solvents are marked "*".

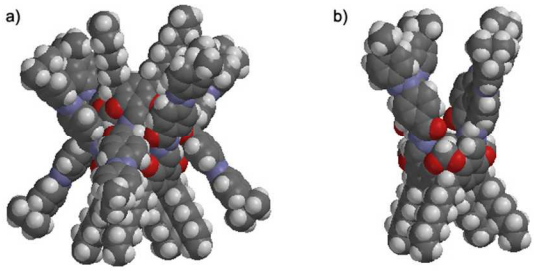


Fig. 7 Energy minimized structures (Semi-Empirical PM3 level, Spartan06 V112) of: a) capsule $\mathbf{2}_2$·8H$^+$, b) cavitand **2**·4H$^+$.

Broken intermolecular hydrogen-bonding of the dissociated cavitand **2**·4H$^+$ caused an upfield shift ($\Delta\delta$ = -0.93 ppm) of the amide N-*H* protons and relatively fast deuterium exchange compared to those of dimeric capsules. Notably, the methine protons (H_i) are observed at 5.50 ppm, which shows that cavitand **2**·4H$^+$ exists as more C_{4v}-symmetric vase confomer than dimeric capsule $\mathbf{2}_2$·8H$^+$.[12] The energy-minimized structure of cavitand **2**·4H$^+$ shows that it prefers a C_{4v}-symmetric vase conformer and four azobenzene moieties are arranged perpendicular to each other (Fig 7). When cavitand **2**·4H$^+$ self-assembles to molecular capsule $\mathbf{2}_2$·8H$^+$, two vase-shaped cavitands should partially open to kite-shaped cavitands to embrace each other, forming strong eight intermolecular hydrogen-bonds and resulting in a downfield shift ($\Delta\delta$ = 0.62 ppm) of H_i in cavitand **2**·4H$^+$.[13] For the same reason, the signals of inner (H_h) and outer (H_j) protons of the dioxymethylene bridge in dissociated cavitand **2**·4H$^+$ were shifted downfield by 0.32 and 0.71 ppm, respectively. The aromatic protons (H_b and H_d) in the

dissociated cavitand $\mathbf{2}\cdot 4H^+$ showed an upfield shift ($\Delta\delta$ = -1.00 and -0.28 ppm) because these protons are located inside the magnetic shielding zone of adjacent azobenzene units. Interestingly, the peaks of heptyl feet in dimeric capsules $\mathbf{2}_2\cdot 8H^+$ are shifted to upfield relative to those of cavitand $\mathbf{2}\cdot 4H^+$ due to the aromatic shielding effect of the long azobenzene pendants of a counter cavitand. The addition of > 8% CD_3OD completely dissociated capsule $\mathbf{2}_2\cdot 8H^+$ to cavitand $\mathbf{2}\cdot 4H^+$ (Fig. 6(c)), and the peak of amide N-*H* disappeared due to the fast deuterium-exchange with CD_3OD. These changes by methanol addition are consistent with UV-Vis experiment and the dissociation process can be observed visually via color change.

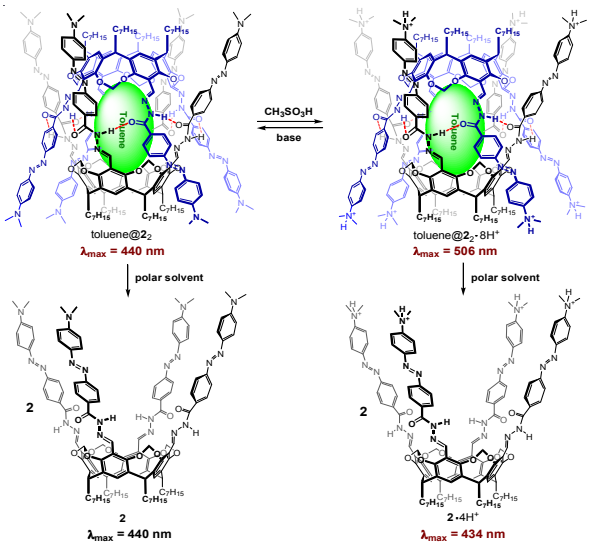


Fig. 8 The assembly and disassembly of a chromogenic molecular capsule.

In summary, a new chromogenic, self-assembled molecular capsule $\mathbf{2}_2$ based on amidoimino-cavitand containing four (*N*,*N*-dimethyl-4-aminophenyl)azobenzyl moieties is characterized. Naked-eye detection of assembly and disassembly of a molecular capsule by tuning the conjugation of amido group with (*N*,*N*-dimethyl-4-aminophenyl)azobenzyl group is expected to promote the research on chromogenic molecular capsules.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedures, characterization data for all the compounds, results of various NMR spectra, UV- and data. See DOI: 10.1039/c000000x/

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