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A new chromogenic, self-assembled molecular capsule G@2 is developed by introducing four \((N,N\text{-dimethyl-4-aminophenyl})\) azobenzyl moieties on the upper rim of a resorcin[4]arene-based amidoimino-cavitand. The tuning of conjugation between amido and \((N,N\text{-dimethyl-4-aminophenyl})\) 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, metal-ligand interactions, hydrophobic interactions, and hybrid noncovalent interactions. The characteristics of their nano-sized cavities as molecular receptor, sensor, reactor, storage, and delivery systems are widely reported.

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.

\(N,N\text{-Disubstituted azobenzene dyes exist in acidic solution as an equilibrium mixture of two tautomers - ammonium form } A \text{ (yellow) and quinoid form } B \text{ (reddish purple).}^{6} \) (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 \(\text{\(^{1}H\) and } \text{\(^{13}C\) 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 \textit{et al.} reported that the relative concentrations of neutral structure \(C\) and dipolar structure \(D\) in acetamide are 60% and 25%, respectively.\(^{10(a)}\) When an amide group hydrogen bonds, the dipolar structure \(D\) becomes favorable.\(^{10(b)}\)

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

\[
\begin{align*}
\text{tautomer A} & \quad \lambda_{\text{max}} = 320 \text{ nm} \\
\text{tautomer B} & \quad \lambda_{\text{max}} = 516 \text{ nm} \\
\text{tautomer E} & \quad \lambda_{\text{max}} = 516 \text{ nm} \\
\end{align*}
\]

We have recently demonstrated that imino-cavitand \(I\) containing four benzamido moieties on its upper rim efficiently self-assembles into thermally inert molecular capsule \(G@I_2\) 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))\(^11\(a)\)

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

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**A chromogenic molecular capsule attributable to dipolar amide resonance structure**

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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 2-8H⁺, c) protonated cavitand 2-4H⁺.

**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 NaNO₂ 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. C₄-symmetric iminocavitand 2 was obtained in 85% yield from the condensation reaction between tetraformyl cavitand 7¹¹ and hydrazide 6 in a mixture of MgSO₄ and dry DMF at room temperature. The structure of cavitand 2 was fully characterized by ¹H NMR, ¹³C-NMR spectroscopy, high-resolution MALDI-TOF mass spectrometry, and elemental analysis.

Cavitand 2 forms a stable molecular capsule, tolune-d₆@2₂, in tolune-d₆, whose structure was confirmed using ¹H 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 tolune@2₂ was investigated through CH₃SO₃H titration in tolune (Fig. 3).

Upon addition of 8.0 equiv. of CH₃SO₃H, the protonated capsule tolune@2₂-8H⁺ shows a distinct hyperchromic effect with 1.7-fold enhancement of ε at λ max = 440 nm compared to that of capsule tolune@2₂ (yellow solution). As more acid was added up to 40.0 equiv., this band (λ max = 440 nm) shifted to 506 nm (Δλ = 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 tolune@2₂-8H⁺ (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/tolune cannot form molecular capsule (Fig. 6(c) and neutral amide resonance C is favorable in this condition (Fig. 2(c)). When CH₃SO₃H was added to a solution of cavitand 2 in 8% methanol/tolune, 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@2:8H+ (Fig. 2(b)) is the
key to its chromogenic phenomena.

**Fig. 4** a) Changes in UV-Vis absorption spectra upon addition of CH3SO2H: a) cavitand 2 (4.7 × 10−5 M in 8% methanol/toluene), b) model compound 3 (1.4 × 10−5 M in toluene).

Fig. 5 shows the UV-Vis absorption shift of the protonated
molecular capsule, toluene@2:8H+ by addition of methanol. As
methanol increases, the band with λmax = 506 nm disappears and a
new blue-shifted (Δλ = -72nm) absorption band with λmax = 434 nm
appears with isosbestic point at 458 nm. This blue shift implies that
the protonated molecular capsule, toluene@2:8H+ dissociates to
cavitand 2:4H+ upon methanol addition, losing electrical conjugation.
As a result, the red color of molecular capsule, 2:8H+ turned yellow.

**Fig. 5** Changes in UV-Vis absorption spectra of toluene@2:8H+ (4.7 × 10−5 M in toluene) upon addition of methanol.

The conversion from capsule to cavitand was also observed in
1H NMR. 1H NMR spectrum of molecular capsule 2:8H+ in toluene-
d4 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 (Hb) and outer (Hi) protons of the dioxymethylene bridge
and methine protons (Hj) 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 CD3OD to
the this molecular capsule solution broke intermolecular amide N–
H···O=C hydrogen bonds due to the competitive hydrogen-bonding
ability of CD3OD, and the conversion from molecular capsule to
cavitand can be observed by 1H NMR spectrum. The 1H NMR
spectrum in the presence of 2% CD3OD (Fig. 6(b)) showed both
signals of dimeric capsule 2:8H+ (black) and dissociated cavitand
2:4H+ (green). Capsule 2:8H+ and cavitand 2:4H+ exist as an
equilibrium mixture in a 62:38 ratio, which is inferred from
comparing 1H NMR integration ratios.

**Fig. 6** 1H NMR spectra (400 MHz) in toluene-d4 at 298 K of: a) toluene-d4@2:8H+ b) after the addition of 2% CD3OD, c) after the addition of 8% CD3OD. [2]j = 5
mM. The signals of capsule 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 2:8H+, b) cavitand 2:4H+.

Broken intermolecular hydrogen-bonding of the dissociated

cavitand 2:4H+ caused an upfield shift (Δδ = -0.93 ppm) of the
amide N-H protons and relatively fast deuterium exchange compared
to those of dimeric capsules. Notably, the methine protons (Hi)
are observed at 5.50 ppm, which shows that cavitand 2:4H+ exists as
more C4-symmetric vase conformer than dimeric capsule 2:8H+.

The energy-minimized structure of cavitand 2:4H+ shows that it
prefers a C4-symmetric vase conformer and four azobenzene
moieties are arranged perpendicular to each other (Fig 7). When
cavitand 2:4H+ self-assembles to molecular capsule 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 (Δδ = 0.62 ppm)
of Hi in cavitand 2:4H+. For the same reason, the signals of inner
(Ha) and outer (Hi) protons of the dioxymethylene bridge in
dissociated cavitand 2:4H+ were shifted downfield by 0.32 and 0.71
ppm, respectively. The aromatic protons (Hb and Hd) in the
dissociated cavitand $2\cdot 4H^+$ 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 $2\cdot 8H^+$ are shifted to upfield relative to those of cavitand $2\cdot 4H^+$ due to the aromatic shielding effect of the long azobenzene pendants of a counter cavitand. The addition of $>8\%$ CD$_2$OD completely dissociated capsule $2\cdot 8H^+$ to cavitand $2\cdot 4H^+$ (Fig. 6(c)), and the peak of amide N-H disappeared due to the fast deuterium-exchange with CD$_2$OD. These changes by methanol addition are consistent with UV-Vis experiment and the dissociation process can be observed visually via color change.

![Image of molecular capsules](image_url)

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

In summary, a new chromogenic, self-assembled molecular capsule $2$, based on amidino-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-Visible data and so forth. See DOI: 10.1039/c0cc00000x/