

Supramolecular Capsule Based on Complementary Adenine-Thymine Base Pairing

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The harmonious effect of multiple hydrogen bonds plays an essential role in the molecular recognition of many biological systems including well-known cases such as the assembly of duplex DNA and the second structure of proteins.¹ In a similar way, multiple hydrogen bonds have been used in the construction of molecular receptors, one-dimensional linear aggregates, two-dimensional planar aggregates, and three-dimensional assemblies.²

Recently, three-dimensional, self-assembled structures have been designed and synthesized based on self-complementary hydrogen bonds.³ Only a few artificial systems, however, have utilized DNA-like, complementary, purine-pyrimidine base pairing for the construction of self-assembled superstructures.⁴ This is because the interaction of adenine (Ade)-thymine (Thy) [or Ade-uridine (Uri)] is too weak ($K_a \approx 10^2 \text{ M}^{-1}$ in CDCl_3),⁵ and because cytosine (Cyt) and guanine (Gua) are notoriously hard to handle due to their poor solubility in organic solvents, despite the strong interaction of Cyt-Gua ($K_a \approx 10^4 \text{ M}^{-1}$ in CDCl_3).⁶ In spite of these limitations, several groups have tried to achieve the desired molecular assemblies by using Ade-Thy [or Ade-Uri] or Cyt-Gua base pairing interactions.⁷

In this report, we describe the self-assembly of a three-dimensional superstructure by using the complementary base-pairing motif. We introduced four Ade and four Thy

units into a resorcin[4]arene cavitand, and constructed a self-assembled molecular capsule *via* multiple hydrogen bonds between the four Ade-Thy pairs in a nonpolar organic solvent (Figure 1).

Construction of three-dimensional molecular assemblies requires that the complementary binding partners meet each other with an appropriate curvature of the hydrogen-bond directionality. In order for the two binding partners to associate with each other by hydrogen bonds, we chose a rather long linker, namely the mercaptopropyl group (*vide infra*).

9-(3-Mercaptopropyl)Ade **1b** and 1-(3-Mercaptopropyl)-Thy **2b** were synthesized from their thiuronium salts (Scheme 1).⁸ Treatment of Ade with 1-bromo-3-chloropropane in the presence of NaH gave 9-(3-chloropropyl)Ade **1a**. Refluxing EtOH solution of **1a** and thiourea and sequential treatment with sodium hydroxide afforded **1b**. 1-(3-Bromopropyl)Thy **2a** was also prepared as shown in Scheme 1. First, Thy was silylated by using hexamethyldisilazane (HMDS) and a catalytic amount of chlorotrimethylsilane (TMSCl). Then, a reaction of the silylated Thy with 1,3-dibromopropane gave **2a**. The last step for the synthesis of **2b** was the same as that of **1b**.

Resorcin[4]arene tetramethylbromide **3** was synthesized using Cram's method.^{9,10} The coupling of **3** and **1b** (or **2b**) was achieved by a typical S_N2 reaction (Scheme 2).

The formation of the self-assembled supramolecular heterodimer between **4a** and **4b** was investigated by ¹H

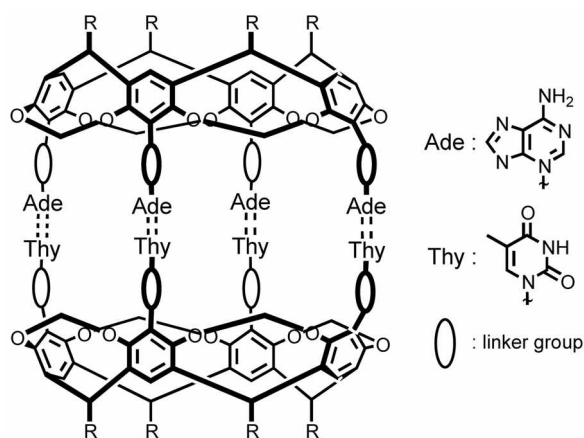
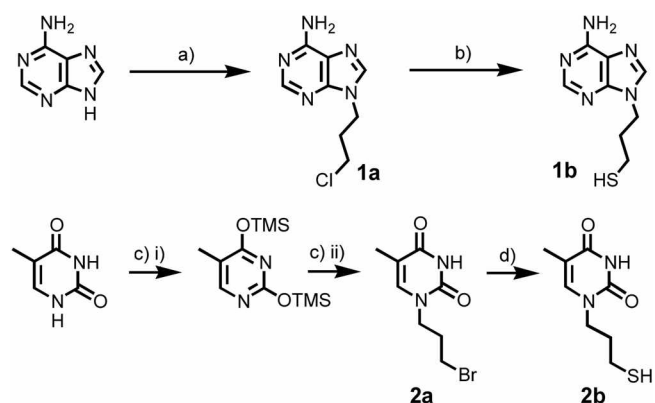
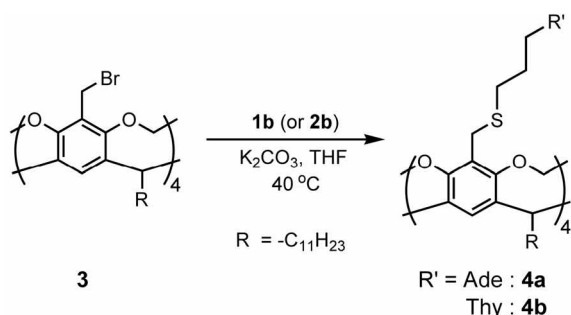


Figure 1. Self-assembled molecular capsule *via* eight hydrogen bonds between four Ade-Thy base pairs.



Scheme 1. Reagents and conditions. a) 1-bromo-3-chloropropane, NaH, DMF, rt., b) thiourea, EtOH, reflux; aq. NaOH, reflux; aq. H⁺, c) i) excess HMDS, cat. TMSCl, reflux, ii) 1,3-dibromopropane, rt., and d) thiourea, EtOH, reflux; aq. NaOH, reflux; aq. H⁺.

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Scheme 2. Synthesis of resorcin[4]arene derivatives **4a** and **4b** with four Ade and Thy units as pendent groups.

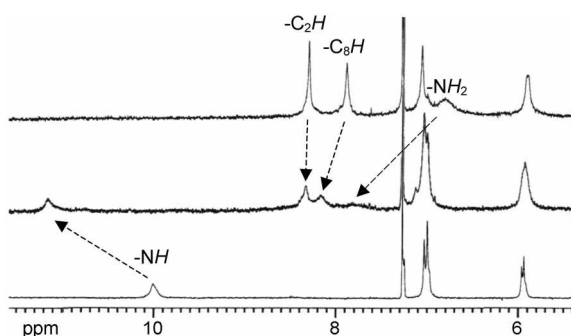


Figure 2. Portion of the ^1H NMR spectra of **4a** (upper), **4b** (lower), and their 1:1 mixture (middle) of **4a** and **4b** (300 MHz, CDCl_3 , 300 K).

NMR spectroscopy. ^1H NMR spectrum of a 1:1 mixture of **4a** and **4b** in CDCl_3 showed the large downfield shifts of the Thy's imide NH (1.26 ppm), the Ade's amino NH (1.00 ppm), and the $\text{C}_8\text{-H}$ (0.28 ppm) of Ade (Figure 2), indicating the formation of a hydrogen-bonded dimeric superstructure. It is also noteworthy that the downfield shift (~ 0.01 ppm) of the Ade's $\text{C}_2\text{-H}$ was much smaller than that of the Ade's $\text{C}_8\text{-H}$, implying that the Hoogsteen hydrogen bonding is the major formation source of the superstructure rather than the Watson-Crick hydrogen bonding.¹¹

The formation of the supramolecular heterodimer was further supported by cold spray ionization mass spectrometry (CSI-MS).¹² The spectrum of an equimolar solution of **4a** and **4b** (Figure 3) exhibited not only the molecular ion peaks of **4a** and **4b** at m/z 2038 ($[\mathbf{4a} + \text{H}]^+$) and 2002 ($[\mathbf{4b} + \text{H}]^+$), respectively, but also the doubly charged signal of the dimeric species formed between **4a** and **4b** at m/z 2020 ($[\mathbf{4a} + \mathbf{4b} + 2\text{H}]^{2+}$). The signals at m/z 2038 and 2002 also indicated the existence of doubly charged homodimeric species because those signals comprised the superimposition of singly and doubly charged signals.¹³

^1H NMR titration study was carried out with the gradual addition of **4a** to the CDCl_3 solution of **4b** (Figure S1). With increasing **4a** addition, the Thy's imide NH signals of **4b** were gradually downfield-shifted ($\Delta\delta_{\text{max}} > 3$ ppm). At a low **4a** concentration, the Ade's amino NH and the $\text{C}_8\text{-H}$ of Ade showed downfield shifts while the $\text{C}_2\text{-H}$ of Ade showed a negligible change. The association constant (K_a) of the hydrogen-bonded supramolecular dimer was obtained by following the chemical shift of Thy's imide NH as a function

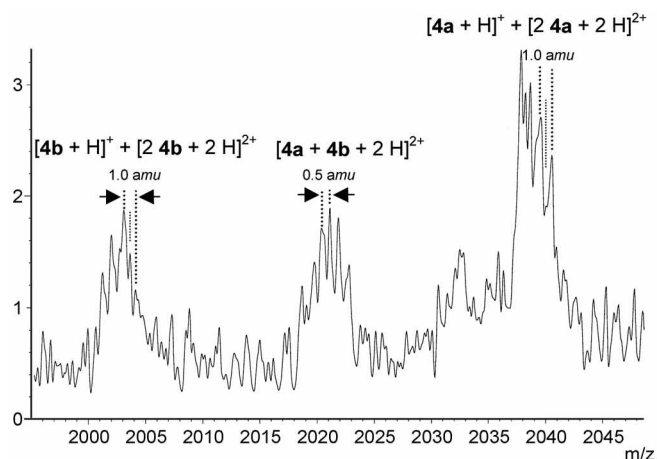


Figure 3. CSI-MS spectrum of a chloroform solution of a 1:1 mixture of **4a** and **4b** (needle voltage: 2.8 kV, needle current: 300–700 nA, orifice voltage: 72 V, ring lens voltage: 110 V, ion source temperature: 253 K, flow rate: 8 $\mu\text{L}/\text{min}$).

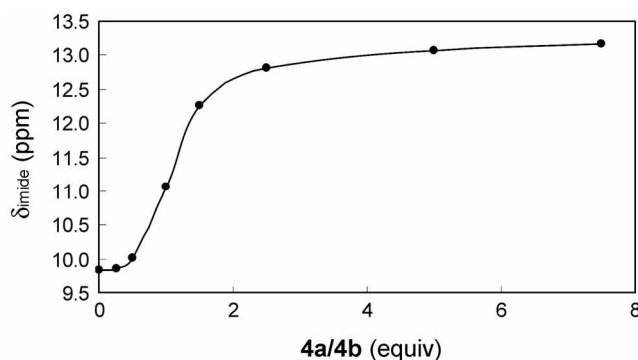


Figure 4. The chemical shift of **4b**'s imide peak as a function of added **4a** ($[\mathbf{4b}] = 1.5$ mM, 300 K).

of the **4a** amount (Figure 4), and by refining the chemical shift values by using nonlinear least-squares fitting methods.¹⁴

Despite the expectation of a large association constant for **4a** and **4b** due to a maximum of eight possible hydrogen bonds between the four Ade and Thy units, K_a was actually estimated to be *ca.* 2300 M^{-1} , allowing for the exclusion of the first part of the titration curve for curve fitting at relatively low $[\mathbf{4a}]/[\mathbf{4b}]$ ratios. Presumably **4a** and **4b** were unable to fully utilize the eight hydrogen bonds simultaneously, due to the excessive flexibility of the two molecules and the high entropic cost of the capsule formation which prevents the simultaneous formation of eight hydrogen bonds. Interestingly, and as noted above, the first part of the titration curve did not fit the typical saturation binding curve: the first part of the titration curve showed small responses to the Ade/Thy ratios. Presumably, this phenomenon was due to the excessive flexibility of the thioether-linker group connecting resorcin[4]arene and the Thy/Ade groups which enabled the formation of intra- or inter-molecular hydrogen bonds between Thy units (or Ade units). When small amounts of **4a** were added to the chloroform solution containing **4b**, they might have disrupted the intra- or inter-molecular Thy-Thy (or Ade-Ade) hydrogen bonds to form more favorable

Ade-Thy pairs. Several neutral guest molecules, such as adamantane, ferrocene, anthracene, phenanthrene and pyrene, showed no ^1H NMR spectroscopic signs of encapsulation within the capsule.¹⁵ This indicates that either there is no driving force for the guest encapsulation or the guests are too small to be encapsulated due to the large portals of the capsule through which these guests can escape.¹⁶

In conclusion, we have demonstrated the synthesis of a self-assembled supramolecular capsule based on the DNA-like, complementary, purine-pyrimidine base pairing. We are currently trying to introduce rigid and short linkers, such as acetylene units, to avoid the intramolecular hydrogen bonds and to introduce small portals.

Experimental Section

Synthesis of cavitand 4a: A mixture of resorcin[4]arene tetramethylbromide **3** (100 mg, 0.065 mmol), K_2CO_3 (100 mg, 0.72 mmol), and 9-(3-mercaptopropyl)Ade **1b** (65 mg, 0.31 mmol) in 5 mL of dry THF was stirred under nitrogen atmosphere at 25 °C for 10 h. The solvent was evaporated under vacuum and the residue was dissolved in 30 mL of CHCl_3 . The resulting solution was washed with water and brine and dried over MgSO_4 . Solvent removal was followed by chromatographic purification on a silica gel column using chloroform and methanol (20:1) to give **4a** (93 mg, 70%). ^1H NMR (300 MHz, CDCl_3): δ 0.90 (t, 12H, $-\text{CH}_3$), 1.1-1.4 (m, 72H, $-\text{CH}_2-$), 2.20 (br, 16H, $-\text{CH}-\text{CH}_2-\text{CH}_2 + \text{CH}_2-\text{CH}_2-\text{CH}_2$), 2.55 (t, 8H, $\text{CH}_2-\text{CH}_2-\text{S}$), 3.59 (s, 8H, Ar- CH_2-S), 4.32 (t, 8H, N- CH_2-CH_2), 4.45 (d, 4H, inner O- CH_2-O), 4.72 (t, 4H, Ar- $\text{CH}-\text{Ar}$), 5.90 (d, 4H, outer O- CH_2-O), 6.93 (br s, 8H, $-\text{NH}_2$), 7.06 (s, 4H, Ar- H), 7.89 (s, 4H, Ade- C_8H), 8.30 (s, 4H, Ade- C_2H); FAB-MS m/z 2038 $[\text{M}+\text{H}]^+$.

Synthesis of cavitand 4b: It was prepared from **3** and **2b** in the same manner as that for cavitand **4a** in 78% yield. ^1H NMR (300 MHz, CDCl_3): δ 0.90 (t, 12H, $-\text{CH}_3$), 1.1-1.4 (m, 72H, $-\text{CH}_2-$), 1.94 (d, 12H, Thy- CH_3), 2.03 (m, 8H, $\text{CH}_2-\text{CH}_2-\text{CH}_2$), 2.16 (br, 8H, $\text{CH}-\text{CH}_2-\text{CH}_2$), 2.60 (m, 8H, $\text{CH}_2-\text{CH}_2-\text{S}$), 3.61 (s, 8H, Ar- CH_2-S), 3.84 (t, 2H, N- CH_2-CH_2), 4.42 (d, 4H, inner O- CH_2-O), 4.74 (t, 4H, Ar- $\text{CH}-\text{Ar}$), 5.95 (d, 4H, outer O- CH_2-O), 7.00 (d, 1H, Thy- C_6H), 7.04 (s, 4H, Ar- H), 9.91 (br s, 4H, $-\text{NH}$); FAB-MS m/z 2002 $[\text{M}+\text{H}]^+$.

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