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Hetero dimer from tetrakisammonium cavitand and tetratopic crown ether cavitand

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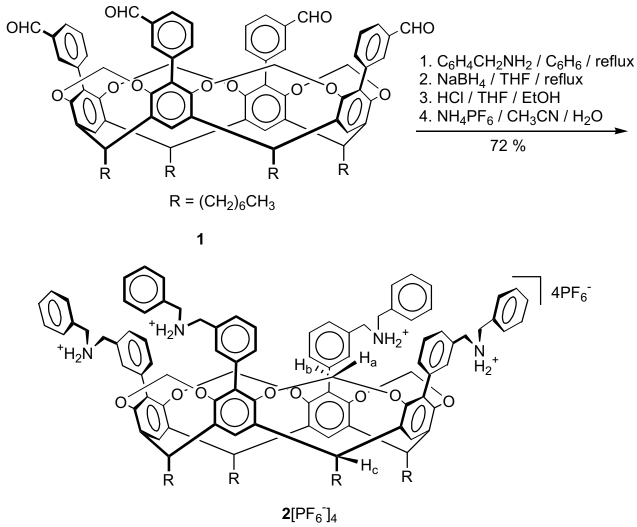
Abstract—Hetero dimer $\mathbf{6}[PF_6^-]_4$ between tetrakis(*m*-ammonium)cavitand $\mathbf{2}[PF_6^-]_4$ and tetrakis(dibenzo-25-crown-8)cavitand **5** was formed in $CDCl_3$ at room temperature. The effects of solvent polarity and temperature on the stability of $\mathbf{6}[PF_6^-]_4$ were studied and the thermodynamic parameters for the formation of $\mathbf{6}[PF_6^-]_4$ are $\Delta G^0_{303\text{ K}} = -6.6\text{ kcal mol}^{-1}$, $\Delta H^0 = -67.4\text{ kcal mol}^{-1}$ and $\Delta S^0 = -201.6\text{ cal mol}^{-1}\text{ K}^{-1}$.

Various self-assembled molecular capsules (SMC)[1] held together by hydrogen bond[2] or metal coordination[3] have been reported. The hydrogen-bonded SMCs were mostly constructed by the dimerization of cyclophane-based cavitands or molecular tweezers capable of complementary hydrogen-bonds each other. When non-covalent interactions act in a multivalent fashion much stronger complexes (both kinetically and thermodynamically) usually result.[4]

Stoddart and co-workers reported various self-assembly systems using hydrogen bonds between ammonium and crown ethers such as molecular daisy chain, artificial photosynthetic center, and dendronized polymers.[5] The hydrogen bond between ammonium and crown ether should be well designed for a supramolecular system due to its bulkiness. When ammoniums or crown ethers were attached on the upper rim of separate cavitands, these two cavitands would self-assemble each other to give a hetero dimer stabilized by tetrakis[2]pseudorotaxane units. If this hetero dimer were stable enough to encapsulate guest molecule or molecules, this would open a new kind of self-assembled molecular capsule.

A [2]pseudorotaxane[6] is a molecule composed of a ring and threading components, which can dissociate into its two components. It would enable the proposed hetero dimer to be dynamically controllable according to temperature, solvent polarity, concentration, and the number of [2]pseudorotaxane units. Here, we report the synthesis of tetrakis(*m*-ammonium)cavitand $\mathbf{2}[PF_6^-]_4$ and tetrakis(dibenzo-25-crown-8)cavitand **5** and the formation of hetero dimer $\mathbf{6}[PF_6^-]_4$ shown in Figure 3.

Cavitand **1**[7] was condensed with benzylamine in a Dean–Stark apparatus to give a tetrakisiminocavitand, which was subsequently reduced ($NaBH_4$/THF) to give a tetrakisaminocavitand. The tetrakisaminocavitand was protonated (HCl/THF/EtOH) and the chloride ions were exchanged ($NaPF_6$/H_2O/CH_3CN) to give



Scheme 1. Synthesis of $\mathbf{2}[PF_6^-]_4$.

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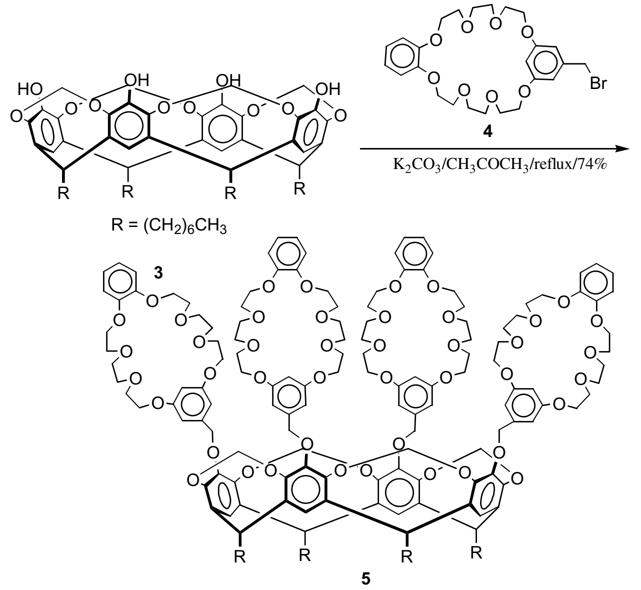
tetrakis(*m*-ammonium)cavitand **2**[PF$_6^-$]$_4$ in 72% overall yield (Scheme 1). The tetrakis(dibenzo-25-crown-8)-cavitand **5** was obtained in 74% yield from tetrol **3** and bromomethyldibenzo-25-crown-8 **4**[5c,8] in a refluxing mixture of K_2CO_3/acetone (Scheme 2). These new compounds were fully characterized by ^{1}H NMR spectroscopy, MALDI-TOF mass spectroscopy, and elemental analyses.

Partial ^{1}H NMR spectra of hetero dimer **6**[PF$_6^-$]$_4$ and its components **2** and **5** are shown in Figure 1. When equimolar amounts (1.4 mM) of **2**[PF$_6^-$]$_4$ and **5** were mixed in $CDCl_3$, only signals for the hetero dimer **6**[PF$_6^-$]$_4$ were observed between 2.5 and 8.0 ppm. The absence of any resonance corresponding to either free **2**[PF$_6^-$]$_4$ or **5** supports a 1:1 complexation between two components. ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC 2D NMR spectra enable to assign the major peaks of complicated spectrum of **6**[PF$_6^-$]$_4$. Figure 2 shows ^{1}H–^{13}C HSQC NMR spectrum for analyzed major peaks of **6**[PF$_6^-$]$_4$. In the Figure 1b, the signal of NH_2^+ protons newly appeared at 7.93 ppm, and the peaks of the outer and the inner protons of OCH_2O bridging units and methine of **2**[PF$_6^-$]$_4$ are shifted from 4.95, 4.22, and 4.76 ppm to 4.32, 3.87 and 4.67 ppm, respectively, upon the formation of **6**[PF$_6^-$]$_4$ (Table 1). The peaks of CH_2N protons of **2**[PF$_6^-$]$_4$ in **6**[PF$_6^-$]$_4$ are separated and shifted downfield to 4.70 and 4.17 ppm from the corresponding peaks of free **6**[PF$_6^-$]$_4$at 4.02 ppm (Fig. 1a). In Figure 1b and c, the signals of the outer and inner OCH_2O bridging protons and methine of **5** in **6**[PF$_6^-$]$_4$ shifted downfield from 5.81, 4.44 and 4.73 ppm to 6.13, 4.57 and 4.82 ppm, respectively. The ethyleneoxy peaks of crown ether moieties of **5** in **6**[PF$_6^-$]$_4$ are separated into 4.27–3.93 and 3.88–2.65 ppm as more complicated peaks. Excess addition of **5** has little influence on the formation of **6**[PF$_6^-$]$_4$. Only the peaks of excess free **5** were newly appeared, which means 1:1 complex **6**[PF$_6^-$]$_4$ is stable on the ^{1}H NMR time scale in solution.



Scheme 2. Synthesis of **5**.

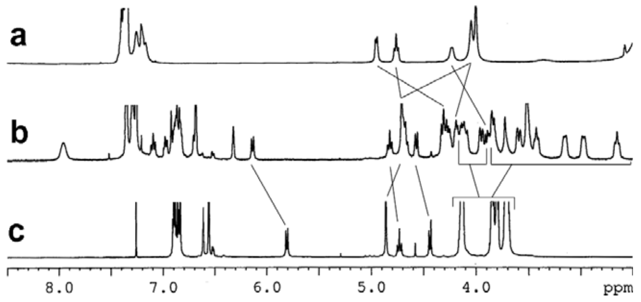


Figure 1. Partial ^{1}H NMR spectra of (a) free **2**[PF$_6^-$]$_4$, 5% DMSO-d_6/$CDCl_3$, (b) **6**[PF$_6^-$]$_4$, $CDCl_3$, (c) free **5**, $CDCl_3$. [**2**[PF$_6^-$]$_4$] = [**5**] = [**6**[PF$_6^-$]$_4$] = 1.4 mM, 400 MHz, 298 K.

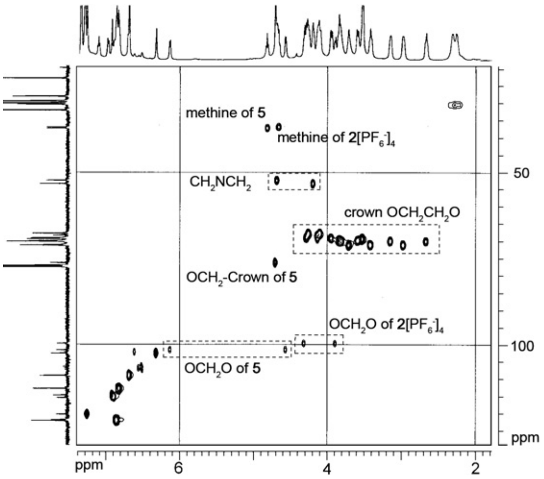


Figure 2. 2D ^{1}H–^{13}C HSQC NMR spectrum of **6**[PF$_6^-$]$_4$ (500 MHz, $CDCl_3$, 298 K).

Figure 4 illustrates the solvent and temperature effects on the stability of **6**[PF$_6^-$]$_4$. Hetero dimer **6**[PF$_6^-$]$_4$ was stable on ^{1}H NMR time scale in $CDCl_3$ at RT (Fig. 4a). In polar solvents such as acetone, MeOH, or DMSO, only free **2**[PF$_6^-$]$_4$ and **5** exist. The separation into two components as increasing the proportions of DMSO-d_6 in the $CDCl_3$ was monitored by ^{1}H NMR spectra (Fig. 4b and c). In Figure 4b, upon the addition 10 μl of DMSO-d_6 to 600 μl of $CDCl_3$ solution of **6**[PF$_6^-$]$_4$ results in a partial dissociation to give free **2**[PF$_6^-$]$_4$ and **5**. Hetero dimer **6**[PF$_6^-$]$_4$, free **2**[PF$_6^-$]$_4$ and **5** were individually observed, indicating that the exchange process is slow on the NMR time scale (Fig. 4b). When 20 μl of DMSO-d_6, was added, capsule **6**[PF$_6^-$]$_4$ was completely separated to free **2**[PF$_6^-$]$_4$ and **5** (Fig. 4c).

The thermodynamic stability of hetero dimer **6**[PF$_6^-$]$_4$ was monitored by ^{1}H NMR experiments between 293 K and 333 K. As Figure 4d shows, the peak at 5.81 ppm of outer dioxymethylene protons of free **5** and the corresponding peak at 6.13 ppm of **6**[PF$_6^-$]$_4$ were coexisted in $CDCl_3$ at 313 K. As temperature increased, the peaks for **6**[PF$_6^-$]$_4$ decreased and those

Table 1. The chemical shifts (ppm) of selected protons in $\mathbf{2}[PF_6^-]_4$, **5**, and $\mathbf{6}[PF_6^-]_4$

Proton	2	5	6 (2)	6 (5)
Outer OCHO	4.95	5.81	4.32	6.13
Methine	4.76	4.73	4.67	4.82
Inner OCHO	4.22	4.44	3.87	4.57
$CH_2NH_2^+CH_2$	4.02		4.70, 4.17	
OCH_2-crown		4.86		4.70
OCH_2O (crown)		4.14, 3.83, 3.80, 3.70		4.27–3.93, 3.88–2.65

500 MHz, $CDCl_3$, 298 K.

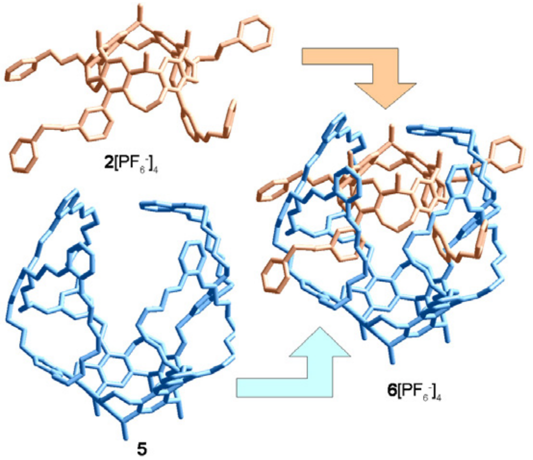


Figure 3. Calculated 3D structures of $\mathbf{6}[PF_6^-]_4$ by Hyperchem 7.5® (MM+ force field). Hydrogens and long alkyl feet are omitted for clarity.

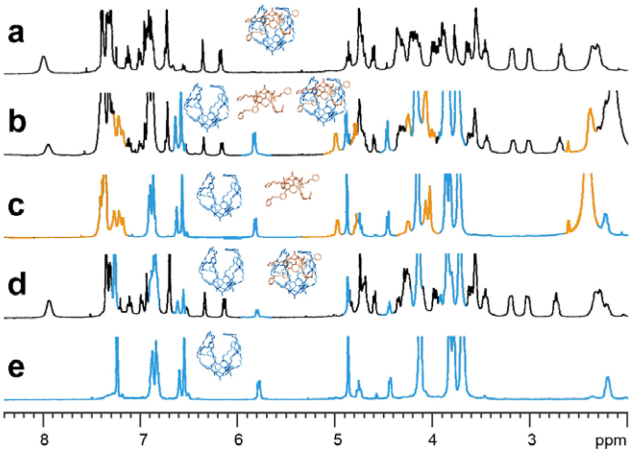


Figure 4. Partial ^1H NMR spectra of $\mathbf{6}[PF_6^-]_4$ (a) $CDCl_3$, (b) 1.6% DMSO-d_6/$CDCl_3$, (c) 3.2% DMSO-d_6/$CDCl_3$, (d) 313 K in $CDCl_3$, (e) 333 K in $CDCl_3$. (a), (b) and (c) 298 K. Resonances are colored as $\mathbf{2}[PF_6^-]_4$ = orange, **5** = blue, $\mathbf{6}[PF_6^-]_4$ = black. $[\mathbf{2}[PF_6^-]_4]$ = [**5**] = $[\mathbf{6}[PF_6^-]_4]$ = 1.4 mM, 400 MHz.

for free **5** increased. Figure 4e at 333 K shows only the peaks of free **5** because decomplexed $\mathbf{2}[PF_6^-]_4$ which is highly insoluble in nonpolar solvents such as $CHCl_3$ and CH_2Cl_2 precipitated. But as the temperature cooled to 298 K, hetero dimer $\mathbf{6}[PF_6^-]_4$ formed again, which implies hetero dimer $\mathbf{6}[PF_6^-]_4$ can be reversibly controlled by temperature.

As shown in Figure 4d, the distinct peaks of hetero dimer $\mathbf{6}[PF_6^-]_4$ (black line) and free **5** (blue line) enable the direct calculation of K_a and then ΔG^0 values as shown in Table 2.[9] The thermodynamic parameters for $\mathbf{6}[PF_6^-]_4$ are $\Delta G^0_{303\ K} = -6.6$ kcal mol^{-1}, $\Delta H^0 = -67.4$ kcal mol^{-1} and $\Delta S^0 = -201.6$ kcal mol^{-1} K^{-1}.

The formation of 1:1 hetero dimer $\mathbf{6}[PF_6^-]_4$ was also supported by the Electron Spray Ionization (ESI) Mass spectrometry. The spectrum in Figure 5 obtained from the solution of equimolar mixture of ammonium cavitand $\mathbf{2}[PF_6^-]_4$ and crown cavitand **5** revealed intense signals at *m/z* 2420, 1566 and 1138 corresponding to the $[\mathbf{6}[PF_6^-]_4 + 2H - 2PF_6^-]^{2+}$, $[\mathbf{6}[PF_6^-]_4 + 3H - 3PF_6^-]^{3+}$ and $[\mathbf{6}[PF_6^-]_4 + 4H - 4PF_6^-]^{4+}$ ions, respectively.

No detectable complexation behavior of hetero dimer $\mathbf{6}[PF_6^-]_4$ for various guest molecules between RT and −40 °C was observed. When large neutral guest (benzene, toluene, xylene, anisole, adamantane, etc.) supposed to be complementary to the cavity of dimer $\mathbf{6}[PF_6^-]_4$ was added to $CDCl_3$ solution of $\mathbf{6}[PF_6^-]_4$ at RT, the peaks of free cavitands **5** and $\mathbf{2}[PF_6^-]_4$ appeared. It is presumable that the pseudorotaxane units of hetero dimer $\mathbf{6}[PF_6^-]_4$ should be reinforced to rotaxane units to enable dimer $\mathbf{6}[PF_6^-]_4$ work as a molecular capsule.

In conclusion, new tetrakis(*m*-ammonium)cavitand $\mathbf{2}[PF_6^-]_4$ and tetrakis(dibenzo-25-crown-8)cavitand **5** were synthesized, and their hetero dimer $\mathbf{6}[PF_6^-]_4$ was formed in $CDCl_3$ solution at room temperature. The effects of solvent polarity and temperature on the stability

Table 2. The binding free energies for the formation of $\mathbf{6}[PF_6^-]_4$ at various temperatures, calculated from ^1H NMR[a] spectrum

Temperature (K)	293	303	313	323
ΔG^{0b} (kcal mol^{-1})	−7.5	−6.6	−5.2	−3.0

[a] 400 MHz, $CDCl_3$.

[b] Ref. 9.

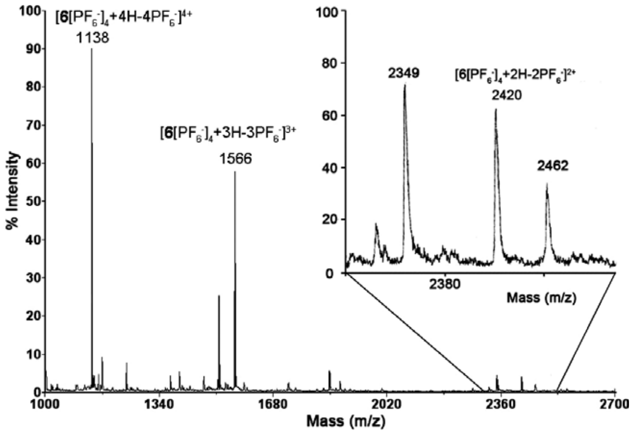


Figure 5. ESI-MS spectrum of $\mathbf{6}[PF_6^-]_4$.

of hetero dimer $\mathbf{6}[PF_6^-]_4$ as well as its thermodynamic parameters were observed.

Acknowledgments

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Supplementary data

General detailed experimental procedures and characterizations data for $\mathbf{2}[PF_6^-]_4$, **4**, **5**. ^1H–^1H COSY NMR spectrum, various temperature experiments data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.005.

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9. $K_a = [\mathbf{6}[PF_6^-]_4]/([\mathbf{2}[PF_6^-]_4]_{free}[\mathbf{5}]_{free})$, $\Delta G^0 = -\mathrm{RTIn}K_a$, $[\mathbf{6}[PF_6^-]_4]$ and $[\mathbf{5}]_{free}$ were calculated directly from ^1H NMR spectra. Precipitated $[\mathbf{2}[PF_6^-]_4]_{free}$ was assumed equal to $[\mathbf{5}]_{free}$, and then $K_a = [\mathbf{6}[PF_6^-]_4]/([\mathbf{2}[PF_6^-]_4]_{free}[\mathbf{5}]_{free})$ was changed to $K_a = [\mathbf{6}[PF_6^-]_4/([\mathbf{5}]_{free})^2$. ΔH^0 and ΔS^0 were calculated from various temperature experiments.