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A "Teflon-Footed" Resorcinarene: A Hexameric Capsule in Fluorous Solvents and Fluorophobic Effects on Molecular Encapsulation**

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Dedicated to Professor Choichiro Hirai on the occasion of his 80th birthday

Supramolecular capsules constructed by the self-assembly of preorganized molecules have attracted considerable attention in recent years.[1] In particular, hydogen-bonded hexameric capsules of pyrogallolarenes and resorcinarenes have been intensively investigated in solution.[2] Interest in hexameric capsules stems from the discovery by MacGillivray and Atwood[3] that *C*-methyl resorcinarene forms a large capsule consisting of six resorcinarene and eight water molecules in the solid state. These supramolecular assemblies have the potential to be used in selective catalysis,[4] drug delivery, and for transport through liquid membranes.

The use of highly fluorinated and perfluorinated (fluorous) solvents and reagents has also grown over the past decade. The unique solubilizing properties of fluorous phases relative to aqueous and common organic phases have solved numerous problems in synthesis, catalysis, and molecular recognition/assembly.[5] Fundamental studies aimed at examining the unusual effects that can be achieved with fluorinated solvents and reagents promise to expand these benefits into new areas.

In this context, it was hypothesized that supramolecular capsules may exhibit more selective and/or enhanced recognition and assembly properties in fluorous solvents because of their fluorophobic effects. The tendency of highly fluorinated molecules to segregate in a fluorous phase, which is both hydro- and lipophobic, is known as the fluorophobic effect.[6] To the best of our knowledge, only a limited number of fluorinated calix[4]arenes[7–11] are known. Furthermore, only one of them is soluble in perfluorohexanes (FC-72) and arises through the formation of reverse F micelles with an average diameter of 25 nm.[8b]

In this study, the first "teflon-footed" resorcinarene ($\mathbf{1}^F$) that is soluble in wet fluorous solvents as a result of the formation of a hexameric capsule was synthesized (Figure 1),

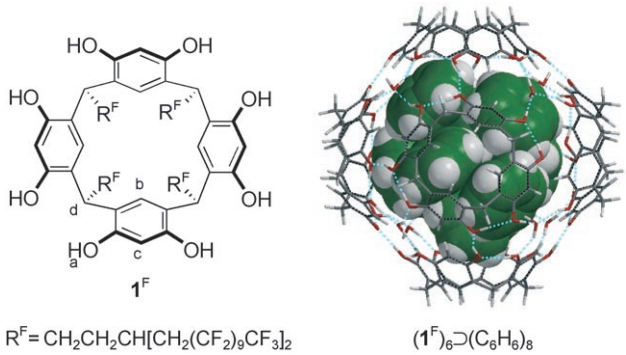
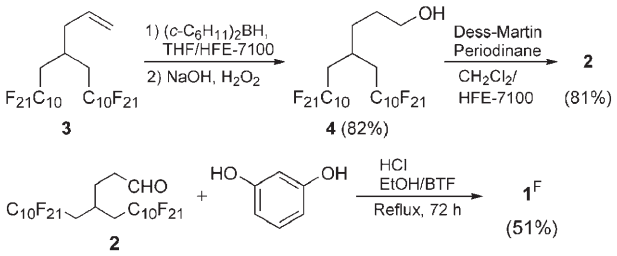


Figure 1. Structure of "teflon-footed" resorcinarene $\mathbf{1}^F$, and model of the hexameric assembly $(\mathbf{1}^F)_6$, which encapsulates eight benzene molecules. Peripheral highly fluorinated alkyl groups (R^F) are not shown for clarity.

which enabled the observation of fluorophobic effects arising from molecular encapsulation in fluorous solvents.

The synthetic strategy employed common cyclooligomerization of resorcinol with highly fluorinated aldehyde **2**, which was prepared from **3** (a homologue of known alkenes[12]) by using a modification of a previously published method[13,14] (Scheme 1). A "teflon-footed" resorcinarene $\mathbf{1}^F$ was obtained



Scheme 1. Synthesis of "teflon-footed" resorcinarene $\mathbf{1}^F$. BTF = benzotrifluoride.

in moderate yields as a crown conformer with all-endo substituents (rccc),[15] as shown by two singlets at $\delta = 7.40$ and 6.21 ppm for H^b and H^c, and one triplet at $\delta = 4.43$ ppm for H^d in the ^{1}H NMR spectrum of $\mathbf{1}^F$ recorded in a mixture of $(CD_3)_2CO$ and C_6F_6 (3:1 v/v).

The "teflon-footed" resorcinarene $\mathbf{1}^F$ was insoluble in common organic solvents such as MeOH, EtOAc, $CHCl_3$, and *n*-C_6H_{14}; whereas it was highly soluble in wet perfluorobutyl methyl ether (HFE-7100) and in wet FC-72. The large partition coefficients in wet FC-72/organic systems, for

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example, 99 with CH_3CN, 124 with EtOAc, 332 with MeOH, indicate that resorcinarene $\mathbf{1}^F$ was substantially immobilized in FC-72, as expected because of its 65.0% fluorine content. The solubility of $\mathbf{1}^F$ in fluorous solvents was improved by the addition of very small amounts of water, which implies that resorinarene $\mathbf{1}^F$ assembles into hexameric capsules in fluorous solvents, in which water molecules play a crucial role. The ^{1}H NMR spectra of $\mathbf{1}^F$ were then measured at 300 K in HFE-7100 solution at different $\mathbf{1}^F/H_2O$ ratios.[16] Only one water signal was observed at all ratios, but the ratio affected the chemical shift of the signal (for details, see the Supporting Information). These observations are essentially the same as those reported by Avram and Cohen[2m] for the formation of hexameric capsules of *C*-undecyl resorcinarene ($\mathbf{1}^H$) with eight water molecules in wet $CDCl_3$.

Moreover, Rebek et al.[2i] demonstrated that hexameric capsules ($(\mathbf{1}^H)_6$)[17] of $\mathbf{1}^H$ in wet, non-deuterated solvents encapsulated six and eight molecules of chloroform and benzene, respectively. In light of these facts, the ^{1}H NMR spectra of $\mathbf{1}^F$ in wet solutions of HFE-7100/benzene containing approximately eight water molecules for six resorcinarene molecules were measured (Figure 2). In wet HFE-7100, the

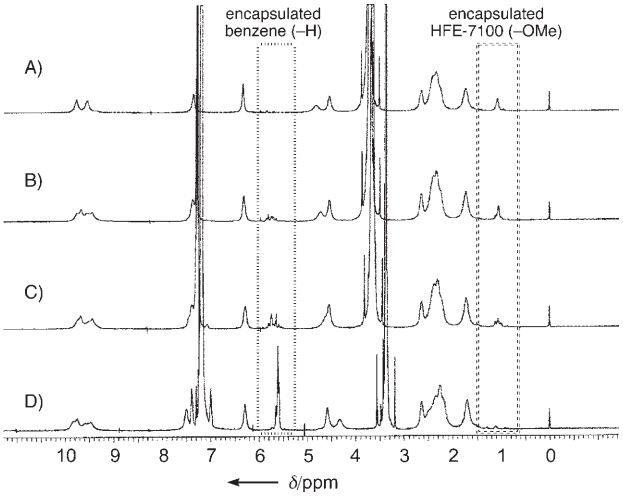

Figure 2. ^{1}H NMR spectra (400 MHz, 300 K) of: A) $\mathbf{1}^F$ (50 mM) in HFE-7100; B) same as (A) after the addition of 2.2 equiv of benzene ($\mathbf{1}^F$, 50 mM), HFE-7100/benzene = 100/1 (v/v); C) same as (A) after the addition of 11 equiv of benzene ($\mathbf{1}^F$, 48 mM), 20/1 (v/v); and D) same as (A) after the addition of 90 equiv of benzene ($\mathbf{1}^F$, 35 mM), 5/2 (v/v).

encapsulated solvent appears at $\delta = 1.1$ ppm, that is, with an upfield shift of about 2.6 ppm (Figure 2A), thus indicating that exchange of guest HFE-7100 molecules in and out of the capsule is slow on the NMR time scale. Integration of the signals showed that an average of 4.3 HFE-7100 molecules were detained in the hexamer. The signal intensity decreased with increasing benzene concentrations, with the encapsulated benzene appearing at 5.5–5.8 ppm and, on average, 7.2 molecules of benzene being detained at a HFE-7100/benzene ratio of 5:2 (v/v) (Figure 2D). This number of benzene molecules corresponds to eight molecules in wet benzene,[2i] since the multiple signals demonstrate that HFE-7100 and/or water molecules were coencapsulated with benzene.[2o] This result confirms the formation of the resorcinarene $\mathbf{1}^F$ hexameric capsule $(\mathbf{1}^F)_6$ in wet fluorous solvents. Furthermore, it is likely that the capsule preferentially encapsulates benzene as a result of fluorophobic effects.

To evaluate the impact of fluorophobic effects on encapsulation, the association constants K_a for the complexation of 3,3-dimethyl-1-butanol (**5**)[18] and *tert*-butylbenzene (**6**) by the hexameric capsule $(\mathbf{1}^F)_6$ were measured by ^{1}H NMR titration experiments in wet HFE-7100. Assuming that the resorcinarene $\mathbf{1}^F$ exists only as hexameric capsules in the fluorous solvent, and that the guests consist of clusters (G_n) with n molecules, Equations (1), (2), and (3) can be derived.

$$(\mathbf{1})_6 + G_n \underset{}{\overset{K_a}{\rightleftharpoons}} (\mathbf{1})_6 \supset G_n \quad (1)$$

$$[G_n] = [G]/n \quad (2)$$

$$[G] = [G]_{total} - n[(\mathbf{1})_6 \supset G_n] \quad (3)$$

Hence, K_a is represented by Equation (4), and, consequently, Equation (5) is obtained. First, the numbers of encapsulated

$$K_a = \frac{[(\mathbf{1})_6 \supset G_n]}{[(\mathbf{1})_6]\,[G]/n} \quad (4)$$

$$\frac{1}{[(\mathbf{1})_6 \supset G_n]} = \frac{n/K_a}{[G]_{total}} \cdot \frac{1}{[(\mathbf{1})_6]} + \frac{n}{[G]_{total}} \quad (5)$$

molecules n were determined to be six and five from analysis of Jobs plots for **5** and **6**, respectively. Six molecules of **5** occupy approximately 57% (ca. 790 Å^3) of the internal volume of about 1375 Å^3[3] and five molecules of **6** occupy approximately 62% (ca. 850 Å^3). The results are quite resonable compared with the optimal value of 55%.[19] Next, the association constants K_a were obtained from the slope of Scatchard plots of $1/[(\mathbf{1}^F)_6 \supset G_n]$ versus $1/[/[(\mathbf{1}^F)_6]$ (Table 1). For comparison, hexameric capsules of *C*-undecyl resorcinarene ($(\mathbf{1}^H)_6$) were also examined in wet $CHCl_3$.

Table 1: Association constants K_a for the complexation of 3,3-dimethyl-1-butanol **5** and *tert*-butylbenzene **6** by $(\mathbf{1}^F)_6$ and $(\mathbf{1}^H)_6$ at 300 K.

Capsule	Solvent	K_a (M^{-1})	
		5	**6**
$(\mathbf{1}^F)_6$	HFE-7100	1.8×10^4	54
$(\mathbf{1}^H)_6$	$CHCl_3$	55	1.1

The association constant K_a of $(\mathbf{1}^F)_6$ for **5** in HFE-7100 is 330-fold larger than that of $(\mathbf{1}^H)_6$ in $CHCl_3$. It is clear that this remarkable difference is due to fluorophobic effects. The K_a value of $(\mathbf{1}^F)_6$ for **6** is 49-fold larger than that of $(\mathbf{1}^H)_6$. It was considered that six molecules of the guest **5**, bearing a primary hydroxy group, are encapsulated by participating in a 60-hydrogen-bond array[2c] on the surface of the capsule and that

hydrogen bonds are strengthened in fluorous solvents. That is to say, fluorophobic effects in the case of **5** arise from the two types of interactions (CH–π and hydrogen bond), which are driving forces for encapsulation. In contrast, only one type of interaction (CH–π and/or π–π) is present for **6**. As a result, the binding ability could be enhanced and very high encapsulation selectivity of guest molecules could be realized in fluorous solvents. To the best of our knowledge, this is the first study that directly evaluates the intensity of fluorophobic effects, rather than indirectly by the measurement of the kinetics of reactions.

Interestingly, the ratio of the hexameric to monomeric forms could be determined from the ^{1}H NMR spectra of a mixture of $\mathbf{1}^F$ and **5** in HFE-7100 solutions with different $\mathbf{1}^F/\mathbf{5}$ ratios while keeping the concentration of **5** constant (70 mM). As shown in Figure 3B ($\mathbf{1}^F/\mathbf{5} = 6/42$), the resonances of H^b and

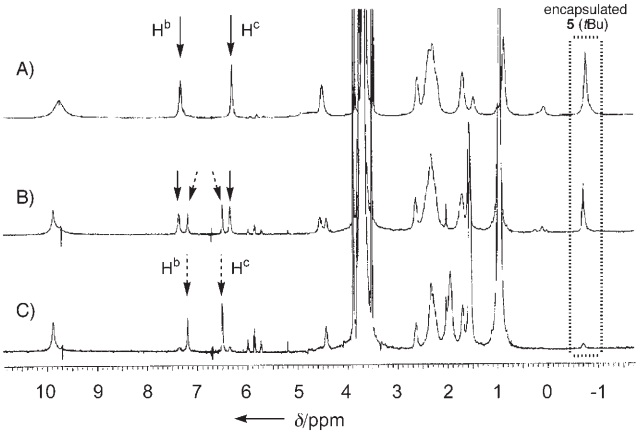

Figure 3. ^{1}H NMR spectra (400 MHz, 300 K) of: A) $\mathbf{1}^F$ (36 mM) and **5** (70 mM) in HFE-7100, $\mathbf{1}^F/\mathbf{5} = 6/12$; B) $\mathbf{1}^F$ (10 mM) and **5** (70 mM), $\mathbf{1}^F/\mathbf{5} = 6/42$; and C) $\mathbf{1}^F$ (3.8 mM) and **5** (70 mM), $\mathbf{1}^F/\mathbf{5} = 6/111$.

H^c in the hexamer of $\mathbf{1}^F$ appeared at approximately $\delta = 7.4$ and 6.4 ppm as two singlets (solid line arrows), respectively. In contrast, those in the monomeric form appeared at approximately $\delta = 7.3$ and 6.6 ppm (dotted line arrows) when the ratio of the hexameric to monomeric forms of $\mathbf{1}^F$ in the mixture was 60:40. This result was supported by the observation that the resonance of the *tert*-butyl group of encapsulated **5** appeared at approximately $\delta = -0.6$ ppm—the point where the hexamer was present (Figure 3A, $\mathbf{1}^F/\mathbf{5} = 6/12$); the resonance disappeared when the hexamer disappeared (Figure 3C, $\mathbf{1}^F/\mathbf{5} = 6/111$). There is only one published example where monomeric and hexameric species have been observed.[2h]

In conclusion, the present study has demonstrated that the synthesis of a "teflon-footed" resorcinarene could be attained by cyclooligomerization of resorcinol with a highly fluorinated aldehyde, and that the fluorous resorcinarene $\mathbf{1}^F$ was soluble in wet fluorous solvents as a result of the formation of hexameric capsules. Moreover, the hypothesis that supramolecular capsules in fluorous solvents exhibit more selective and/or enhanced properties as a result of fluorophobic effects through encapsulation was verified. The system using "teflon-footed" resorcinarene capsules as nanoreactors or carriers may provide new options for synthetic chemistry and process engineering. Future studies will focus on organic reactions in the capsule and on separation through liquid membranes using the capsule as a carrier.

Experimental Section

$\mathbf{1}^F$: Resorcinol (0.250 g, 2.27 mmol) and the highly fluorinated aldehyde **2** (2.58 g, 2.27 mmol) were dissolved in a mixed solvent of ethanol (5.0 mL) and benzotrifluoride (7.2 mL), and concentrated hydrochloric acid (0.46 mL) was added under argon. After heating the mixture at reflux for 72 h, FC-72 (20 mL) and water (10 mL) were added, and the fluorous layer was washed with water (2×10 mL) and with methanol (3×10 mL). The fluorous layer was concentrated, and the residue was purified by passing it through a column of silica gel with hexane/EtOAc/HFE-7100 (6:3:1) and then hexane/EtOAc/HFE-7100/2-PrOH (22:67:7:4) as eluents to give $\mathbf{1}^F$ (1.43 g, 0.291 mmol, 51%) as a yellow solid. $R_f = 0.15$ (hexane/EtOAc/HFE-7100/2-PrOH, 69:23:7:1 (v/v)); m.p. 158 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO/C_6F_6$, 3:1 (v/v)) $\delta = 8.52$ (s, 8H), 7.40 (s, 4H), 6.21 (s, 4H), 4.43 (t, $J = 7.4$ Hz, 4H), 2.37–2.70 (m, 28H), 1.72–1.84 ppm (m, 8H); partial ^{13}C NMR (100 MHz, $(CD_3)_2CO/C_6F_6$, 2:1 (v/v)) $\delta =$ 153.9, 125.1, 125.0, 104.7, 35.9 (t, $J_{CF} = 20.6$ Hz), 35.2, 34.6, 32.1, 26.9 ppm; IR (KBr): $\tilde{\nu} = 3250$, 2946, 2874, 1621, 1503, 1445, 1205, 1114, 901, 710 cm^{-1}; elemental analysis calcd for $C_{128}H_{58}F_{168}O_8 \cdot 1.4H_2O$ (4915.56): C 31.13, H 1.20; found: C 31.15, H 1.47.

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