Supplementary Material (ESI) for Chemical Communications

Solvent Denaturation of Supramolecular Capsules Assembled via the Hydrophobic Effect

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Supplementary Material

Experimental section

General.

All reagents were purchased from Aldrich and were used without purification. Host **1** was synthesized as previously reported.[1] Trioxolanes **2a**-**d** (Figure S1) were synthesized and purified by chromatography according to previous reported methods.[2] NMR spectra were recorded on a Varian 400 or a Varian Inova 500 MHz spectrometer. Chemical shifts are reported relative to $CDCl_3$ (7.26 ppm) or $(CD_3)_2SO$ (2.50 ppm). MALDI-MS spectra were collected using a Bruker-Daltonics MALDI-TOF Autoflex III mass spectrometer. Elemental analysis was performed by Atlantic Microlab Inc.

Characterization of trioxolane 1b

Colorless oil. R_f = 0.41 (Hexane/Ether, 50:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) ™ 2.01 – 1.85 (m, 10H), 1.85 – 1.80 (m, 1H), 1.80 – 1.77 (m, 1H), 1.75 –1.64 (m, 1H), 1.64 – 1.56 (m, 9H). MS (MALDI): Calcd. 251 $[M + H]^+$, Found: 215 $[M + H]^+$. Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86 Found: C, 71.67; H, 8.84.

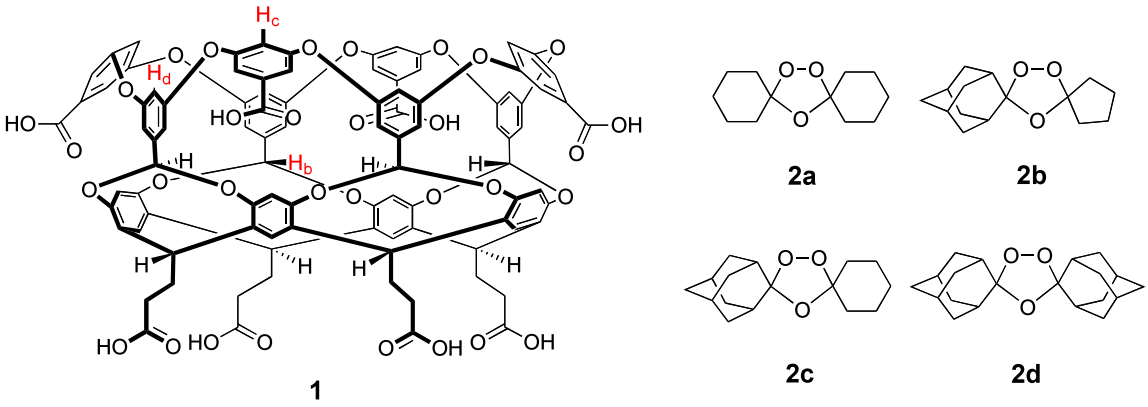

Figure S1: Chemical structures of host **1** and trioxolanes **2**.

^{1}H NMR spectra for the capsular complexes between 1_2 and trioxolane 2a-d

All NMR titration were recorded on an Inova-500 MHz spectrometer with the addition of a DMSO guest solution to the host solution (1.0 mM host **1** in 10 mM $Na_2B_4O_7/D_2O$ solution). Trioxolane **1d** was noted to be totally insoluble in water, but was dissolved in aqueous solutions of the host. Figures S2-S5 show that only 2:1 capsule formed between the host and guests **2a**-**d**. Important host atoms labeled in the figures are highlighted in Figure S1. COSY NMR was used to assign all protons (proton b, c, d are the protons on host **1**; those protons shift significantly when host **1** binds with guests).

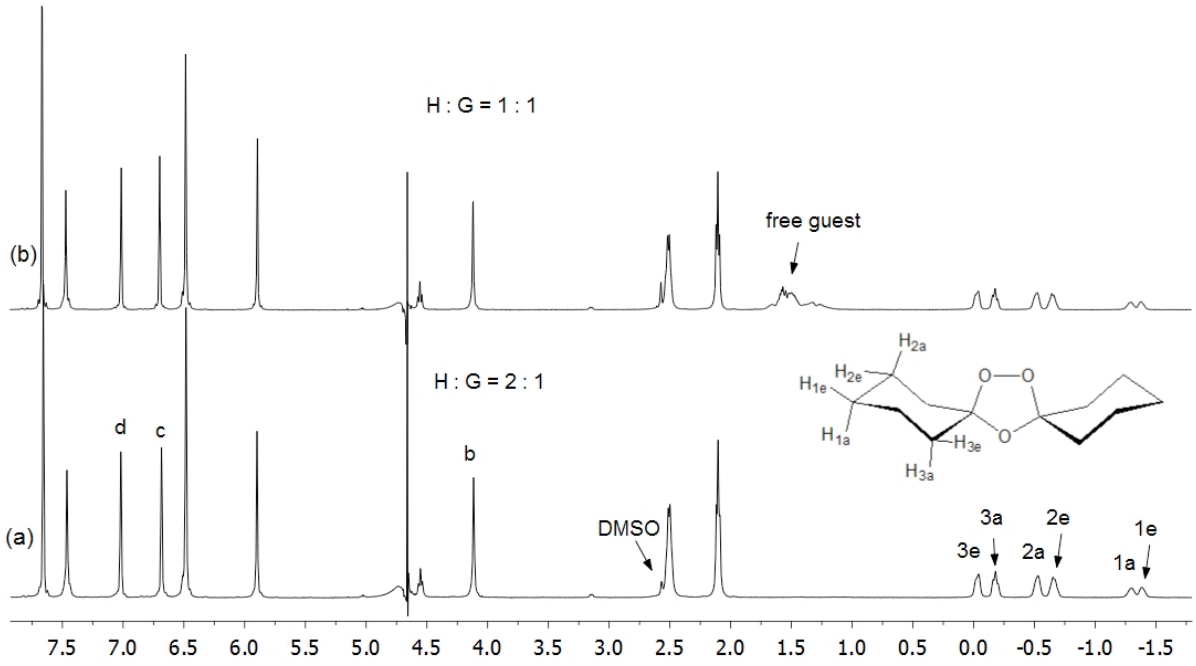

Figure S2: ^{1}H NMR of the 2:1 capsule formed between **1** and trioxolane **2a**.

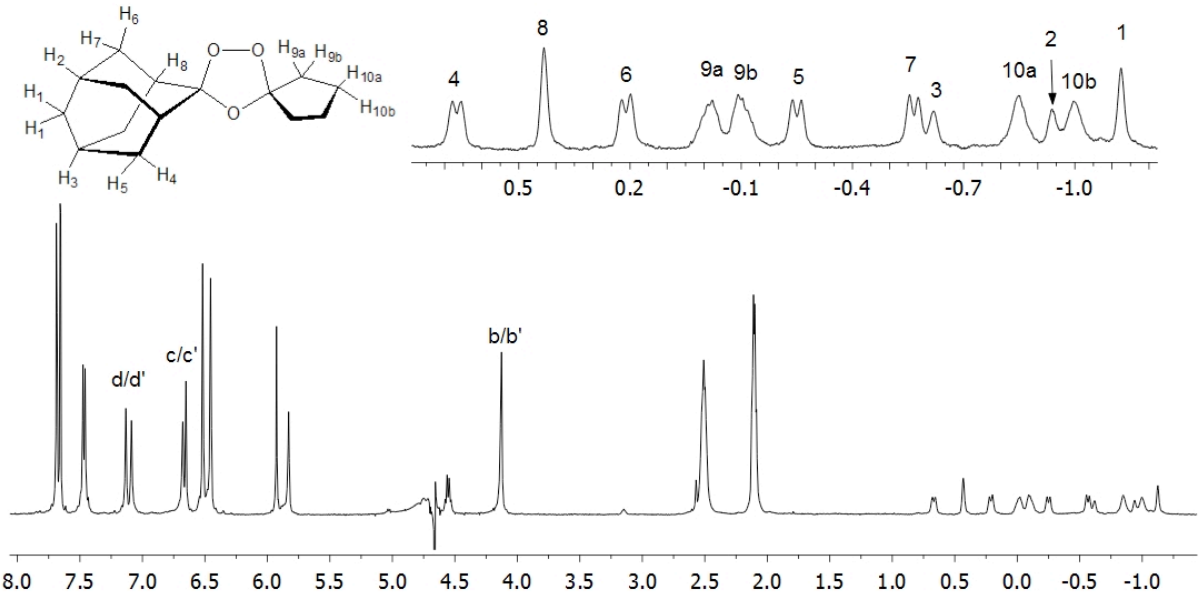

Figure S3: ^{1}H NMR spectrum of the 2:1 capsule formed between **1** and trioxolane **2b**.

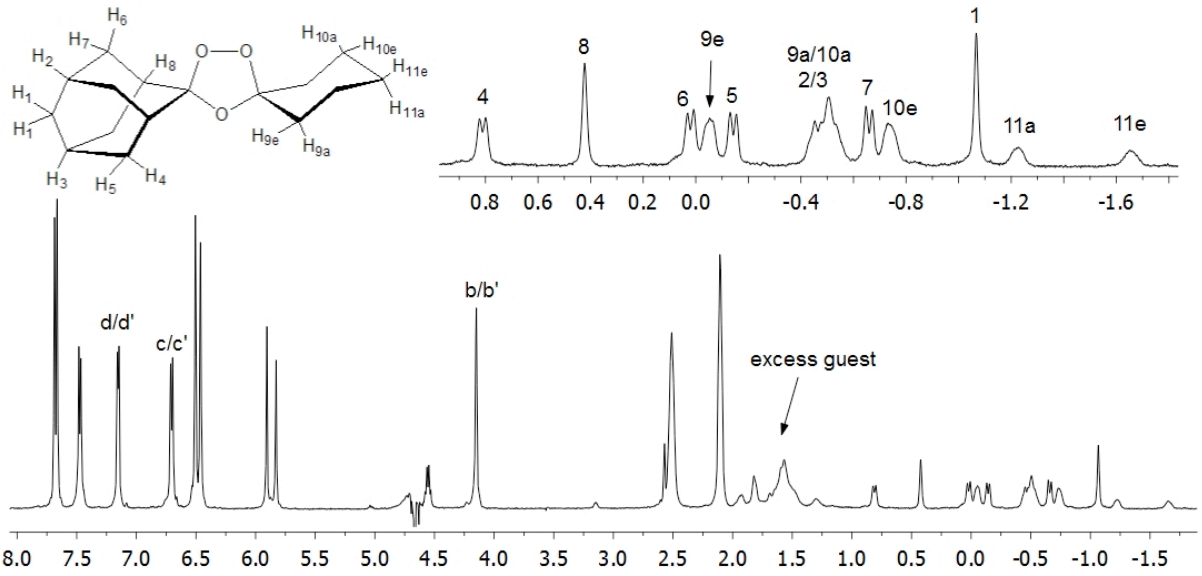

Figure S4: ^{1}H NMR spectrum of the 2:1 capsule formed between **1** and trioxolane **2c**.

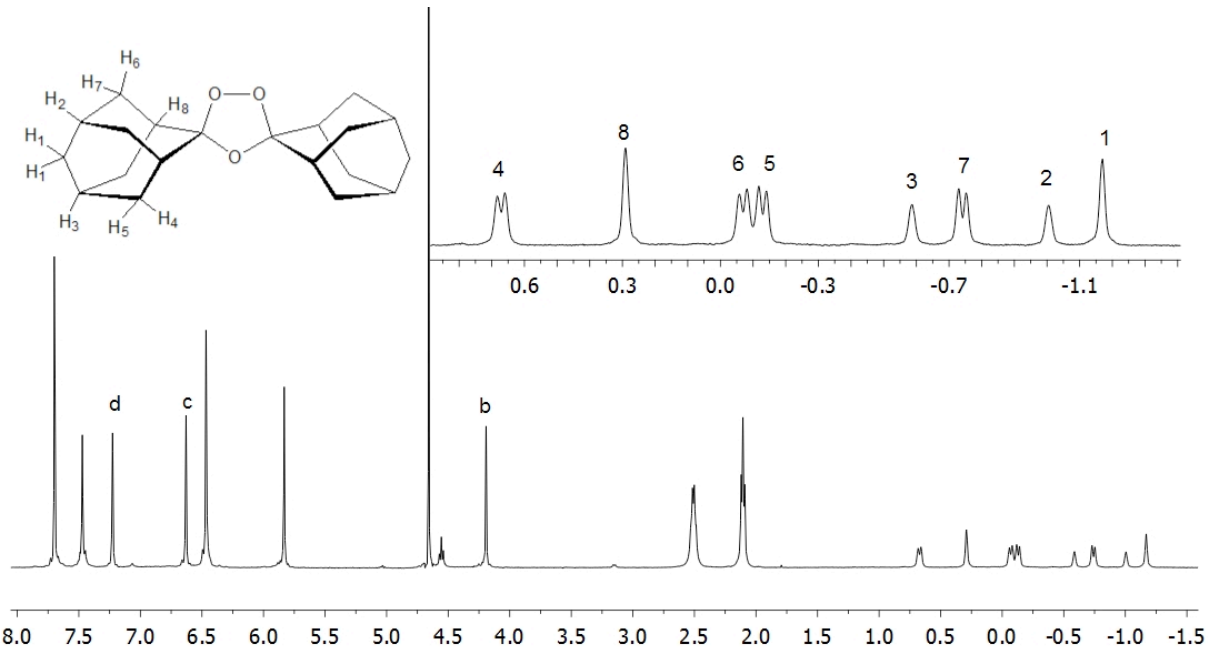

Figure S5: ^{1}H NMR spectrum of the 2:1 capsule formed between **1** and trioxolane **2d**.

Selected COSY/NOESY NMR data for encapsulated trioxolanes 2a-d

Figures S6-S10 show COSY/NOESY NMR for encapsulated trioxolanes **2a**-**d** (only guest region shown). Every guest protons were assigned according to these NMR (see Figure S2-S5 for all assignment).

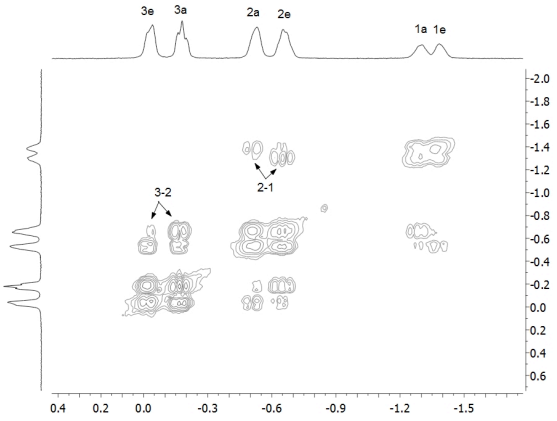

Figure S6: COSY NMR of encapsulated **2a**.

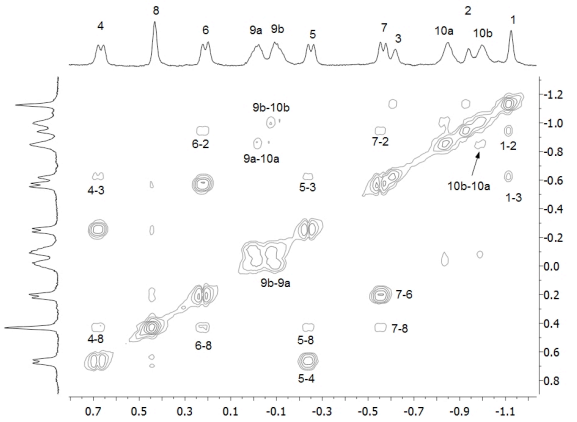

Figure S7: COSY NMR of encapsulated **2b**.

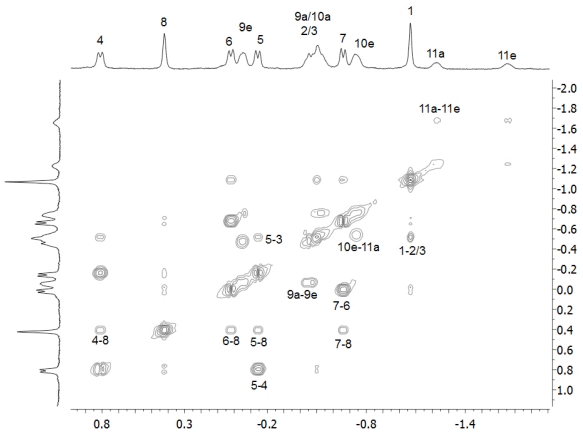

Figure S8: COSY NMR of encapsulated **2c**.

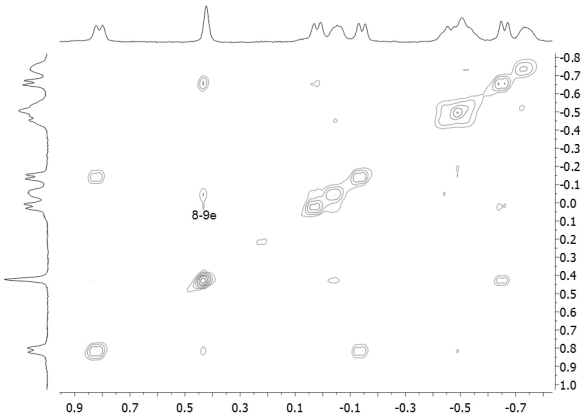

Figure S9: NOESY NMR of encapsulated **2c.**

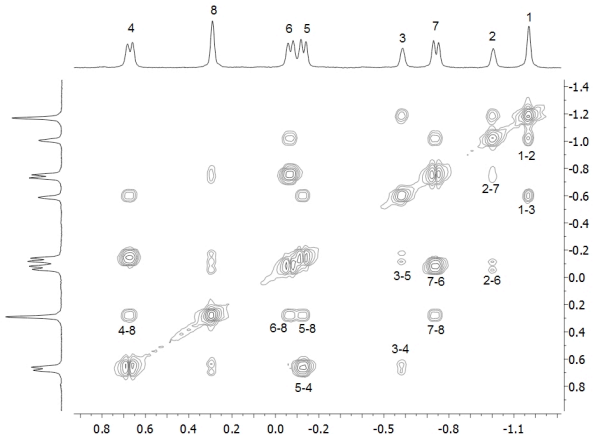

Figure S10: COSY NMR of encapsulated **2d.**

Denaturation of 2:1 the capsular complex involving trioxolane 2b

All NMR experiments were carried at 5 °C (at rt the peaks were broad and peak integration problematic in the presence of organic solvents) in 10 mM $Na_2B_4O_7/D_2O$ with the addition of (deuterated) organic solvents. The starting concentrations of both host and guest were 1.0 mM, so at the beginning of the titration only half the guest was bound (as a 2:1 capsular complex). The percentage of species in the solution was calculated by integrating selected peaks. Figures S11-S17 and Table 1 (main text) show the distribution of 2:1 capsule, 1:1 complex and free guest as a function of the volume of solvent added.

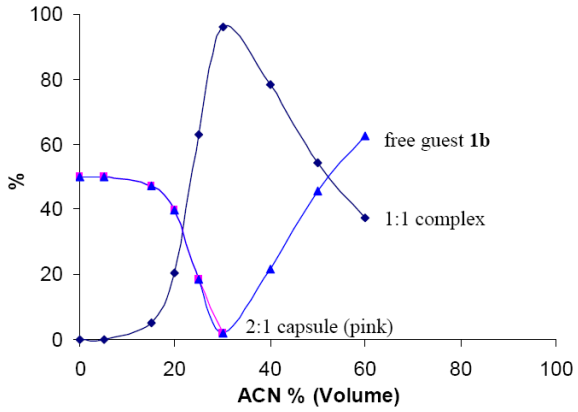

Figure S11: Denaturation of the capsular complex of **2b** with addition of MeCN.

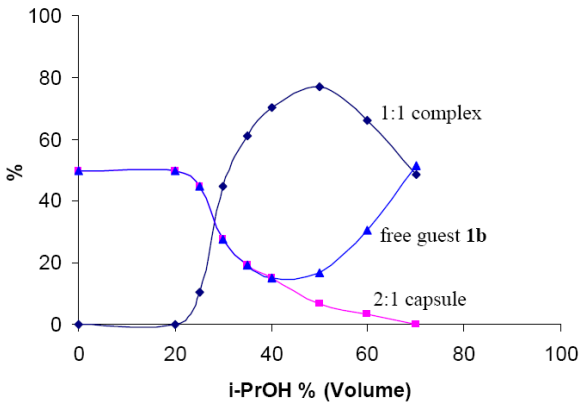

Figure S12: Denaturation of the capsular complex of **2b** with addition of i-PrOH.

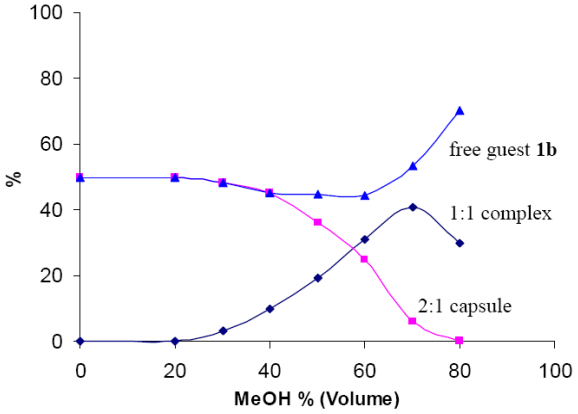

Figure S13: Denaturation of the capsular complex of **2b** with addition of MeOH.

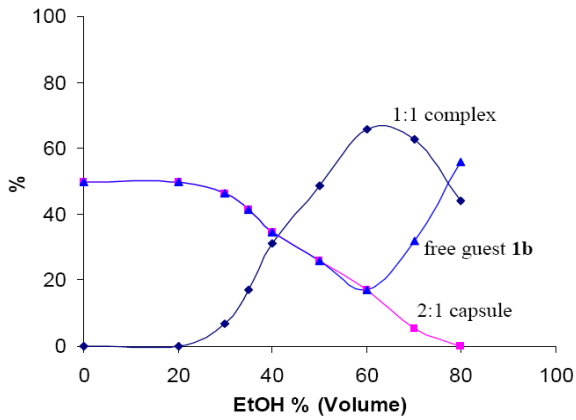

Figure S14: Denaturation of the capsular complex of **2b** with addition of EtOH.

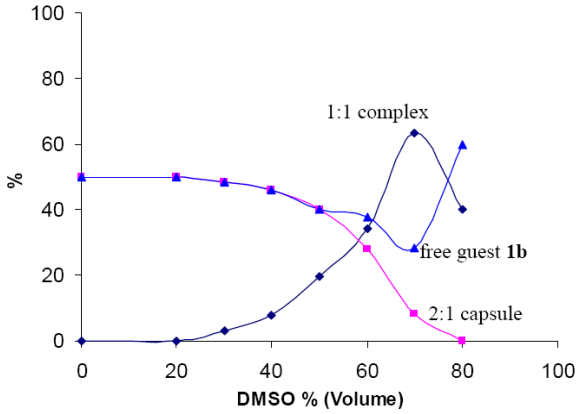

Figure S15: Denaturation of the capsular complex of **2b** with addition of DMSO.

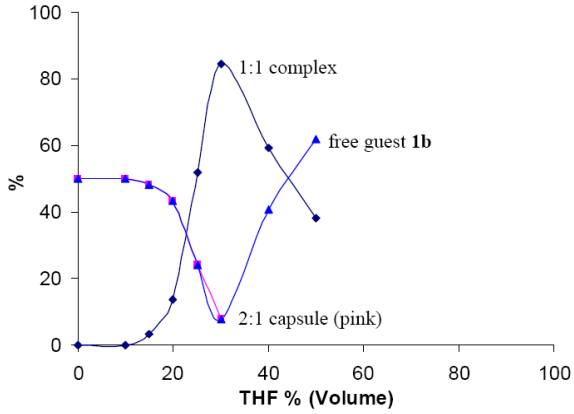

Figure S16: Denaturation of the capsular complex of **2b** with addition of THF.

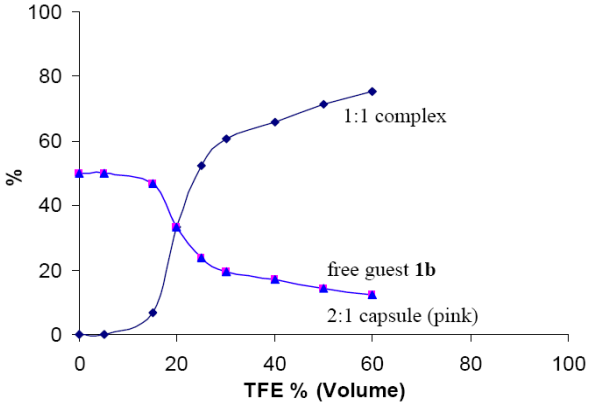

Figure S17: Denaturation of the capsular complex of **2b** with addition of TFE (Trifluoroethanol).

Apparent binding constant for the capsular complex involving trioxolane 2b

In order to demonstrate that denaturation was not a result of dilution during the titration with organic solvents, a dilution experiment using pure water were carried out. The 2:1 capsular complex of **2b** with **1** (starting concentrations: [$\mathbf{1}_2$] = [**2b**] = 0.5 mM) was diluted with D_2O to 0.1 mM. ^{1}H NMR showed no evidence of breakdown of the 2:1 capsular complex at this concentration. According to the following equation, the minimum, apparent binding constant can be easily estimated.

$$\mathbf{1}_2 + 2\mathrm{b} \underset{}{\overset{K_{app}}{\rightleftharpoons}} \mathbf{1}_2\cdot 2\mathrm{b}$$

$$K_{app} = [\mathbf{1}_2\cdot 2\mathrm{b}] / ([\mathbf{1}_2]\,[2\mathrm{b}])$$

Thus, if we assume that less than 5% disassembly of the capsule occurred, then in the equilibrated solution the concentrations of the different species are: [$\mathbf{1}_2$] = [**2b**] = 0.005 mM, [$\mathbf{1}_2$•**2b**] = 0.095 mM. This gives a minimum K_{app} = 3.8 × 10^6 M^{-1}. If on the other hand we assume that less than 2% disassembly of the occurred then the concentrations of the different species are: [$\mathbf{1}_2$] = [**2b**] = 0.002 mM, [$\mathbf{1}_2$•**2b**] = 0.098 mM, and a minimum K_{app} = 2.5 × 10^7 M^{-1} can be calculated.

Denaturation of capsular complexes formed between 1 and 2a, 2c and 2d

For guests **2a** and **2c** Figures S18-S19 show the distribution of all species as a function of the volume of acetone added. The limited solubility of guest **2d** prevented an analogous titration with this guest.

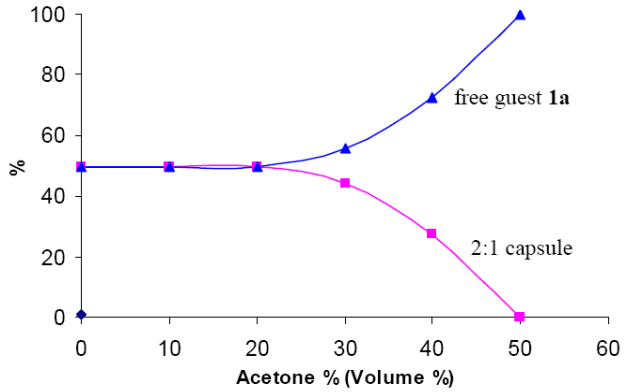

Figure S18: Denaturation of the capsule **2a** with addition of Acetone.

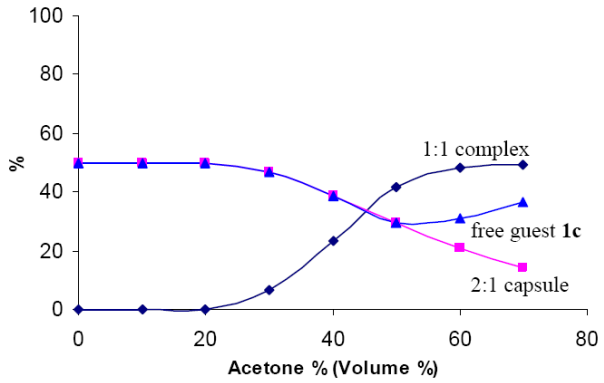

Figure S19: Denaturation of the capsule **2c** with addition of Acetone.

References

1. *Well Defined, Organic Nano-Environments in Water: The Hydrophobic Effect Drives a Capsular Assembly*. Gibb, C. L. D. & Gibb, B. C. *J. Am. Chem. Soc.* **2004**, *126*, 11408-11409.

2. *Identification of an antimalarial synthetic trioxolane drug development candidate*. Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Santo Tomas, J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004**, *430*, 900–904.