A gemini guest triggers the self-assembly of a calixarene capsule in water at neutral pH

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General information

The host **TAC4** was obtained according to the procedure described by Gutsche *et al.*¹ Since accurate determination of the binding constants requires concentrations to be precisely known, the purity of **TAC4** was determined *via* thermogravimetric analysis (TGA) and potentiometry, as described previously.² The adsorbed residual water amounts to 9-10% of **TAC4** weight; **TAC4** fully decomposed at T<500°C indicating that the host is free from inorganic impurities.

The concentration of **BS2** and **TAC4** (*vide infra*) was obtained by correcting for the water amount determined via TGA.

All the chemicals were obtained from Sigma Aldrich and used as received, after drying. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck 60, F254). All reactions were carried out under nitrogen atmosphere unless otherwise stated. High purity water (Millipore, Milli-Q Element A 10 ultrapure water) and A grade glassware were employed throughout.

The distribution diagram as well as the mole fraction values was obtained with HySS.³

NMR experiments

NMR experiments were carried out at 27 °C on a 500 MHz spectrometer (¹H at 499.88 MHz, ¹³C at 125.7 MHz) equipped with a pulse field gradient module (Z axis) and a tunable 5 mm Varian inverse detection probe (ID-PFG); chemical shifts (δ) are expressed in ppm and are referenced to residual deuterated solvent. NMR data were processed using the MestReC software.⁴

NMR titrations were performed by mixing **BS2** and **TAC4** in the appropriate ratios in D₂O (**BS2** concentration fixed at 2.5×10^{-4} mol dm⁻³; phosphate buffer 2.5×10^{-2} mol dm⁻³). The chemical shifts corresponding to all the **BS2** resonances collected in the H/G 1-8 range were simultaneously fitted using HyperNMR;⁵ this ensured that the amount of complex formed ranged from 20 to 80% of the total guest concentration.

NMR diffusion measurements were performed using the bipolar pulsed gradient stimulated echo (BPPSTE or BBPLED due to the long eddy-current delay) Varian pulse sequences⁶ and were processed by the Varian DOSY software incorporated in VNMR. Data were acquired with a 75 ms diffusion delay in all experiments, with a bipolar gradient pulse duration of 2 ms. For all

experiments, 25 different gradient amplitudes were used, until a 90% decrease in the resonance intensity was achieved. A fixed concentration of **BS2** (0.25 mmol dm⁻³) was used while the concentration of **TAC4** varied from 0.25 mM to 2.00 mM.

The diffusion coefficients were extracted from the formula:

 $\ln(I/I_0) = -\gamma^2 \,\delta^2 \,G^2 \,(2/\pi)^2 \,(\Delta - \delta \,/\, 4) \,D = -b \,D$

where *I* and I_0 are the echo intensities in the presence and absence of gradient pulse, respectively, γ is the gyromagnetic ratio, *G* is the pulse gradient strength, $2/\pi$ is a geometrical connection factor due to the sine-shape of the pulse gradients used, δ is the length of the pulse gradient, Δ is the time interval between the leading edges of the pulse gradient used and *D* is the diffusion coefficient.

Two-dimensional ROESY experiments were performed using Varian standard pulse sequences.

ITC titrations

The data for determination of the thermodynamic parameters were obtained using a nanoisothermal titration calorimeter Nano-ITC^{2G},⁷ with an "active" cell volume of 0.986 mL at 25 °C in water (phosphate buffer, pH 6.8).

Since the ¹H NMR studies indicated that the encapsulation process was fast all ITC titrations were run by setting the time interval to 300 sec. ITC measurements were carried out by titrating an aqueous solution of **BS2** (1.9-3×10⁻³ mol dm⁻³) into a **TAC4** solution ($4.4\times10^{-4} - 1\times10^{-3}$ mol dm⁻³); both the host and the guest were dissolved in 0.1 mol dm⁻³ phosphate buffer (pH = 6.8). Six independent experiments were run. The heats of dilution were determined in separate experiments by titrating the solution of the guest (in phosphate buffer) into a solution containing phosphate buffer only. The net heat obtained was fit using Hyper Δ H,⁸ that allows for the simultaneous fitting of data from multiple titrations.

ESI-MS experiments

Electrospray ionization mass spectra (ESI-MS) were recorded on a Finnigan LCQ Deca XP ion trap (Thermo Fischer Scientific, USA) using an electrospray ionization (ESI) interface.

Buffered solutions (pH \sim 7, phosphate buffer) containing appropriate ratios of the host and the guest were introduced into the ESI source via a 100 μ m i.d. fused silica capillary, using a 500 μ l

syringe. The experimental conditions for spectra, acquired in positive ion mode, were as follows: needle voltage 4.5 kV; flow rate 3-5 μ l/min; source temperature 250 °C; m/z range 50-4000; cone potential -38 V; tube lens offset -55 V.

Synthesis



Scheme S1 Synthesis of BS2.

Synthesis of 1,1'-[ethane-1,2-diylbis(oxy)]bis(4-methylbenzene) (2)

1,2-dibromoethane (0.43 ml, 5.0 mmol) was added to a stirred suspension of 4-methyl-phenol **1** (1.04 ml, 10.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) in acetonitrile (60 mL). After 18 hours of stirring at 50 °C, the mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. After solvent removal, the residue was dissolved in CH₂Cl₂ and washed with water. The organic layer was evaporated to dryness and the resulting precipitate was purified by re-crystallization from methanol (0.77 g, 3.2 mmol, 64%).

NMR: $\delta_{\rm H}$ (500 MHz, CDCl₃, 27 °C) 7.08 (d, ³*J*(H,H)= 8.9 Hz, 4H; ArH); 6.82 (d, ³*J*(H,H)= 8.9 Hz, 4H; ArH); 4.13 (t, ³*J*(H,H)= 7.5 Hz, 4H; OCH₂); 2.29 (s, 6H; ArH); $\delta_{\rm C}$ (125 MHz,

CDCl₃, 27 °C) 159.05, 130.05, 129.83, 114.27, 69.73, 29.36 ppm. ESI-MS *m*/*z* : 265 (100%) [*M*+Na⁺].

Synthesis of 2,2'-[ethane-1,2-diylbis(oxy)]bis(5-methylbenzenesulfonic acid) (BS2)

2 (0.50 g, 2.1 mmol) was added to H_2SO_4 96% (1.0 ml) kept at 0 °C. The suspension was stirred at RT for 1 hour. The solvent was removed by vacuum filtration, and the residue washed with ethyl acetate. The orange solid was purified by re-crystallization from methanol to yield the gemini-like guest (0.78 g, 1.93 mmol, 92%).

NMR: $\delta_{\rm H}$ (500 MHz, D₂O, 27 °C) 7.53 (s, 2H; ArH); 7.28 (d, ³*J*(H,H)= 8.5 Hz, 2H; ArH); 7.13 (d, ³*J*(H,H)= 8.5 Hz, 2H; ArH); 4.43 (t, ³*J*(H,H)= 7.1 Hz, 4H; OCH₂) 2.20 (s, 6H; CH₃); $\delta_{\rm C}$ (125 MHz, D₂O, 27 °C) 153.26, 133.72, 130.98, 130.08, 128.36, 115.10, 68.32, 19.48 ppm. ESI-MS *m*/*z*: 200 (100%) [*M*²⁻].



Fig. S1 Complexation induced shift (CIS) diagram: plots of $\Delta\delta$ observed (ppm) versus H/G ratio (D₂O, phosphate buffer, pD=7.1, 25°C).



Fig. S2 HyperNMR output for the CH_3 (top) and H_3 (bottom) proton signals (\circ and \diamond : experimental points, solid line: theoretical fit for the HG (a) and the HG+H₂G (b) model).



Fig. S3 Calorimetric titration of **TAC4** ($4.5 \times 10^{-4} \text{ mol dm}^{-3}$) with **BS2** ($3.0 \times 10^{-3} \text{ mol dm}^{-3}$).



Fig. S4 Species distribution under the conditions employed for ITC experiments; $C^{\circ}_{TAC4} 4.4 \times 10^{-4} \text{ mol dm}^{-3}$.



Fig. S5 Species distribution under the conditions employed for NMR experiments. $C_{BS2}^{\circ} 2.5 \times 10^{-4} \text{ mol dm}^{-3}$.



Fig. S6 Optimized model (arrows indicate the spatially correlated groups).



Fig. S7 2D ROESY interactions (phosphate buffer, D_2O , pD 6.8, TAC4/BS2 = 3.6).

Diffusion coefficients

Diffusion coefficients (DOSY experiments) have been determined as reported previously.9

	MW	D _{calcd}	D _{extrapolated} *	Hydrodynamic radius**
		$(\times 10^{\cdot 10} \text{ m}^2 \text{ s}^{\cdot 1})$	$(\times 10^{-10} \text{ m}^2 \text{ s}^{-1})$	(× 10 ⁻¹⁰ m)
TAC4	652.1	3.1	3.1 (1)	6.4 (2)
BS2	402.2	4.4	4.4 (1)	4.6 (1)
TAC4:BS2 (1:1)	1053.2	3.2	3.3 (1)	6.1 (2)
TAC4 ₂ :BS2 (2:1)	1706.0	2.8	2.6 (1)	7.7 (3)
*σ in parenthesis;				
** Calculated from the Stokes–Einstein equation assuming a spherical entity $(D=K_bT/(6\pi\eta r_s))$.				

 Table S1 Theoretical and extrapolated diffusion coefficients and hydrodynamic radii for the species in solution.

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