Guest-induced Capsule Formation Based on Concerted Interactions in Water at Neutral pH

Carmela Bonaccorso, Antonio Ciadamidaro, Carmelo Sgarlata,‡ Domenico Sciotto* and Giuseppe Arena*

Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Viale Andrea Doria 6, 95125 Catania, Italy. Fax: +39 (0)95 337678;
E-mail: garena@unict.it, dsciotto@unict.it.
‡Current address: Lawrence Berkeley National Laboratory, 1 Cyclotron Road Berkeley, CA 94720, USA.

Supporting Information

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 **BS** 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 (^{1}H at 499.88 MHz, ^{13}C NMR at 125.7 MHz) equipped with a pulse field gradient module (Z axis) and a tunable 5mm 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 **BS** and **TAC4** in the appropriate ratios in NMR tubes in D_2O (**BS** concentration fixed at 2.5×10^{-4} mol dm^{-3}; phosphate buffer $2,5\times10^{-2}$ mol dm^{-3}). The chemical shifts corresponding to all the **BS** resonances collected in the H/G 1-10 range were simultaneously fit 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 sequences[6] 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 **BS** (0.25 mmol dm^{-3}) was used while the concentration of **TAC4** varied from 0.25 mM to 2.50 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

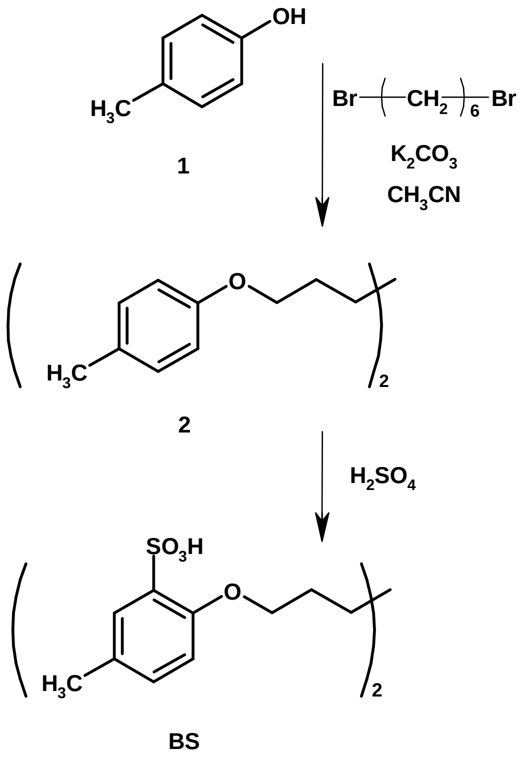
The data for determination of the thermodynamic parameters reported in Table 1 were obtained using a nano-isothermal titration calorimeter Nano-ITC^{2G} [7] with an "active" cell volume of 0.986 mL at 25 °C in water (phosphate buffer, pH 6.8).

Since the ^{1}H 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 **BS** (5×10^{-4}-10^{-3} mol dm^{-3}) into a **TAC4** solution ($3.9x10^{-4}$-2.84×10^{-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 HyperΔH,[8] that allows for the simultaneous fitting of data from multiple titrations.

ESI-MS measurements

ESI mass spectra were registered on a HP 1100 equipment (Series LC/MSD) using water as the solvent. **BS** concentration was 10 μM. For the analysis of the mixture **TAC4**/**BS** ratio was 4.

Synthesis



Scheme S1. Synthesis of **BS**

Synthesis of 1,1'-[hexane-1,6-diylbis(oxy)]bis(4-methylbenzene) (**2**)

1,6-dibromohexane (0.77 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 acetone (100 mL). After 12 hours of stirring at 50 °C, the mixture was allowed to cool to room temperature and then the solvent was removed under reduced pressure. After solvent removal, the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was evaporated to dryness and the resulting precipitate was purified by re-crystallization from methanol (2.1 g, 7.3 mmol, 73%).

NMR: δ_H (500 MHz, $CDCl_3$, 27°C) 7.08 (d, ^3J(H,H)= 8.9 Hz, 4H; ArH); 6.80 (d, ^3J(H,H)= 8.9 Hz, 4H; ArH); 3.95 (t, ^3J(H,H)= 7.5 Hz, 4H; OCH_2) 2.29 (s, 6H; ArH) 1.80 (m, 4H; CH_2) 1.54 (m, 4H; CH_2); δ_C (125 MHz, $CDCl_3$, 27°C) 158.45, 129.90, 129.83, 113.07, 67.89, 28.84, 25.73, 20.54 ppm. ESI-MS *m*/*z* : 321 (100%) [M+Na^+].

Synthesys of 2,2'-[hexane-1,6-diylbis(oxy)]bis(5-methylbenzenesulfonic acid) (**BS**)

2 (1.13 g, 3.7 mmol) was added to (2.5 ml) of H_2SO_4 96% 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 (1.45 g, 3.2 mmol, 86%).

NMR: δ_H (500 MHz, D_2O, 27°C) 7.46 (s, 1H; ArH); 7.18 (d, ^3J(H,H)= 8.7 Hz, 1H; ArH); 6.90 (d, ^3J(H,H)= 8.7 Hz, 1H; ArH); 3.99 (t, ^3J(H,H)= 7.1 Hz, 4H; OCH_2) 2.16 (s, 6H; ArH) 1.70 (m, 4H; CH_2) 1.40 ppm (m, 4H; CH_2); δ_C (125 MHz, D_2O, 27°C) 153.52, 133.49, 129.79, 129.77, 128.35, 113.76, 68.84, 28.10, 25.59, 19.41 ppm. ESI-MS *m*/*z*: 228 (100%) [M^{2-}].

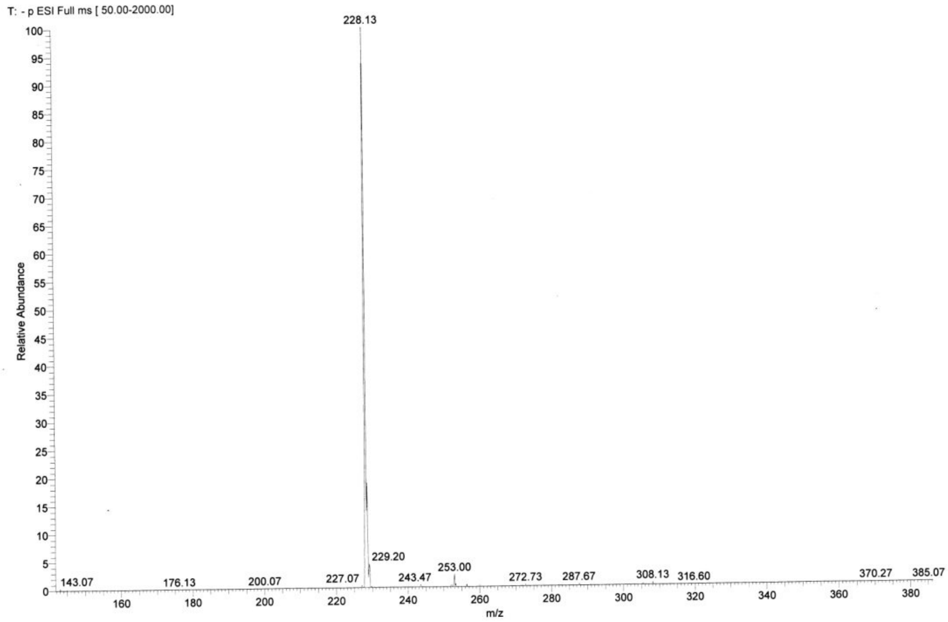


Figure S1. ESI-MS spectrum of
2,2'-[hexane-1,6-diylbis(oxy)]bis(5-methylbenzenesulfonic acid)

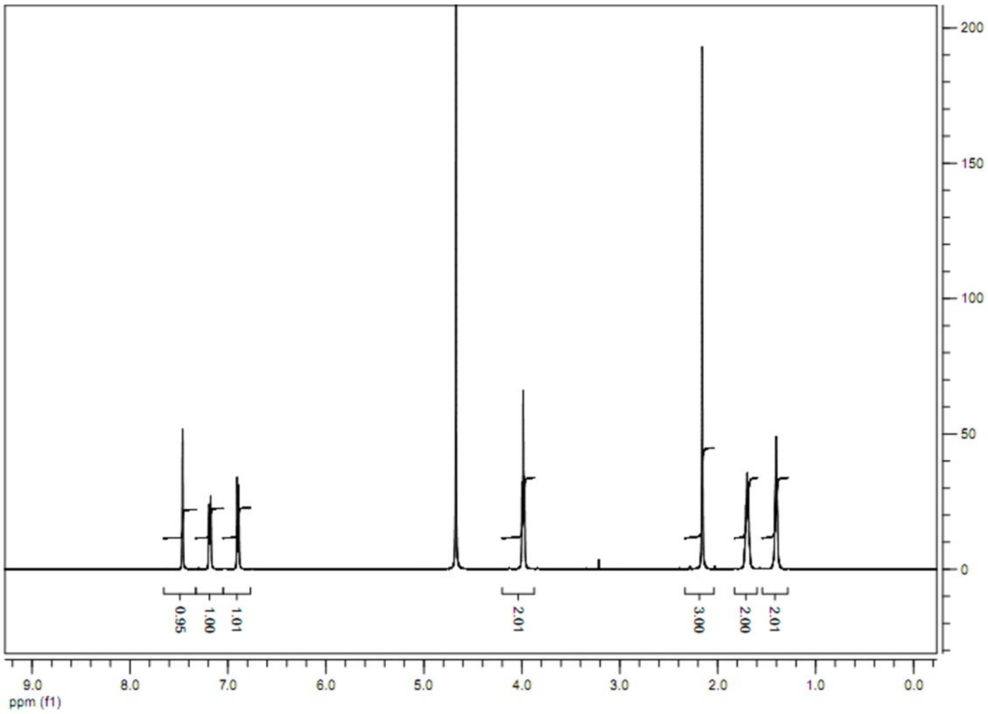


Figure S2. ^{1}H-NMR spectrum of
2,2'-[hexane-1,6-diylbis(oxy)]bis(5-methylbenzenesulfonic acid)

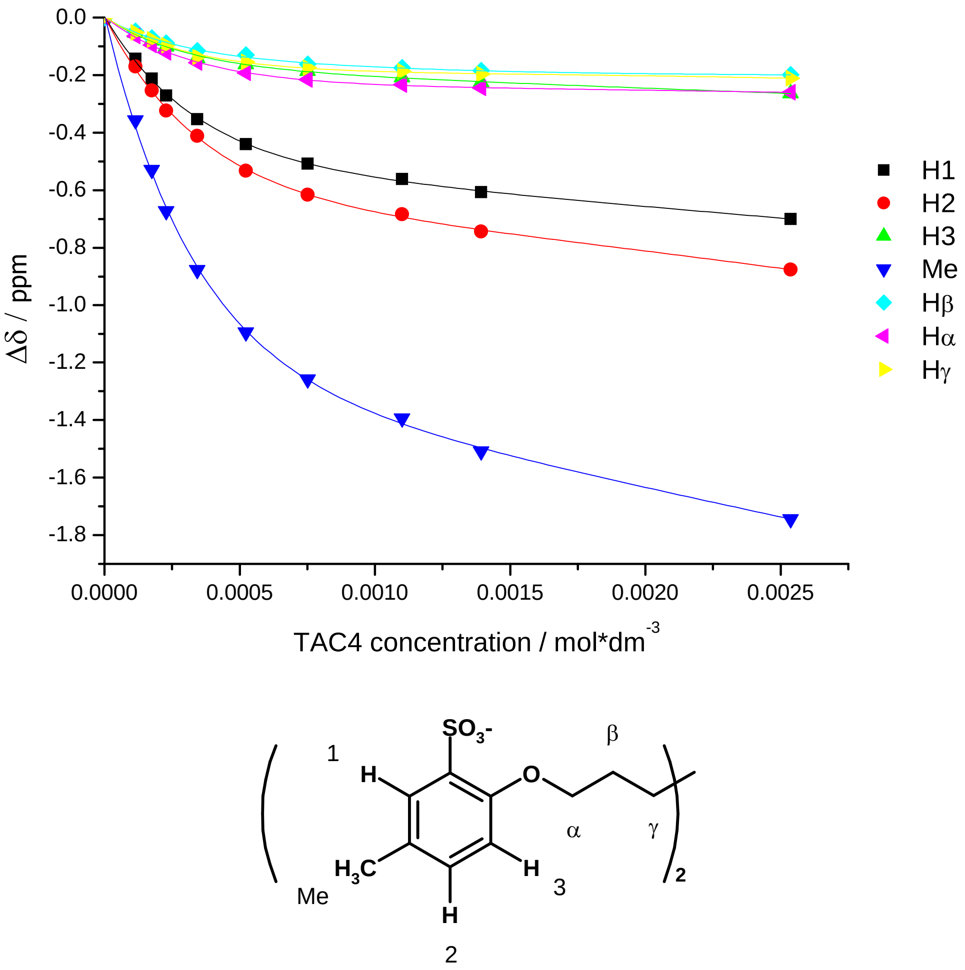
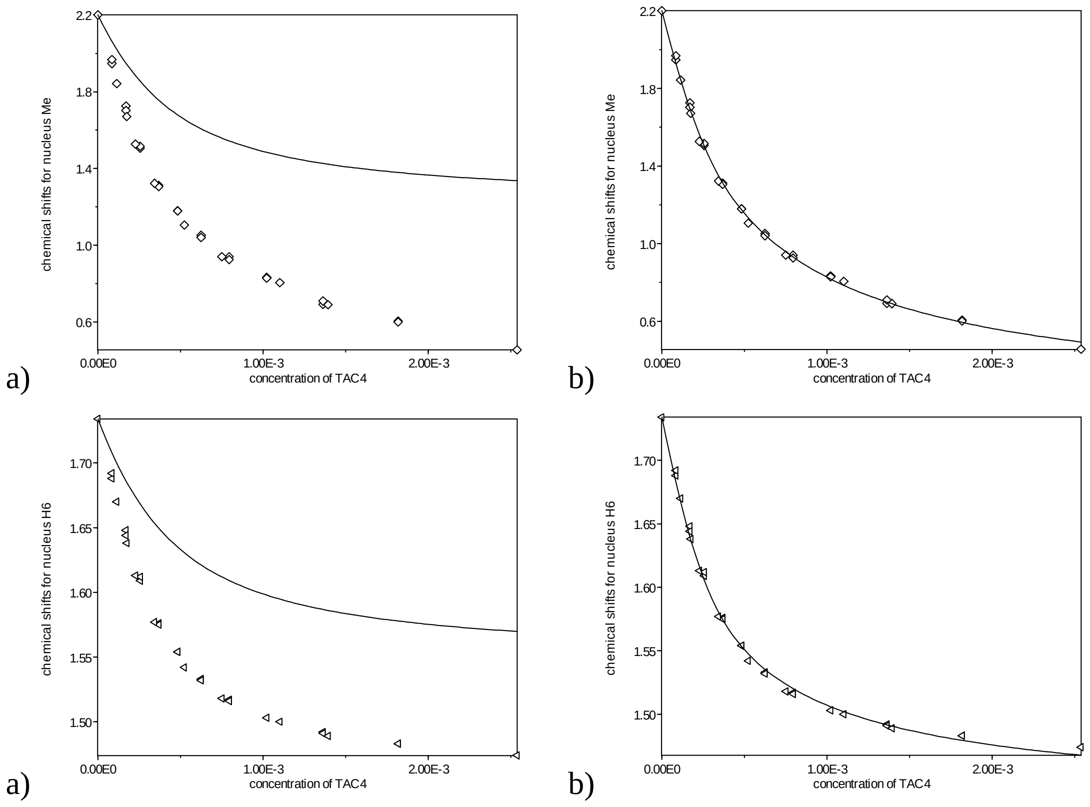


Figure S3. Observed Complexation Induced Shifts (Δδ, ppm) *vs* **TAC4** concentration.



a: HG model

b:HG+H_2G model

Figure S4. HyperNMR output for the Me (top) and Hβ (bottom) proton signals (◊ and Δ: experimental points, solid line: theoretical fit for the HG (a) and the HG+H_2G (b) model).

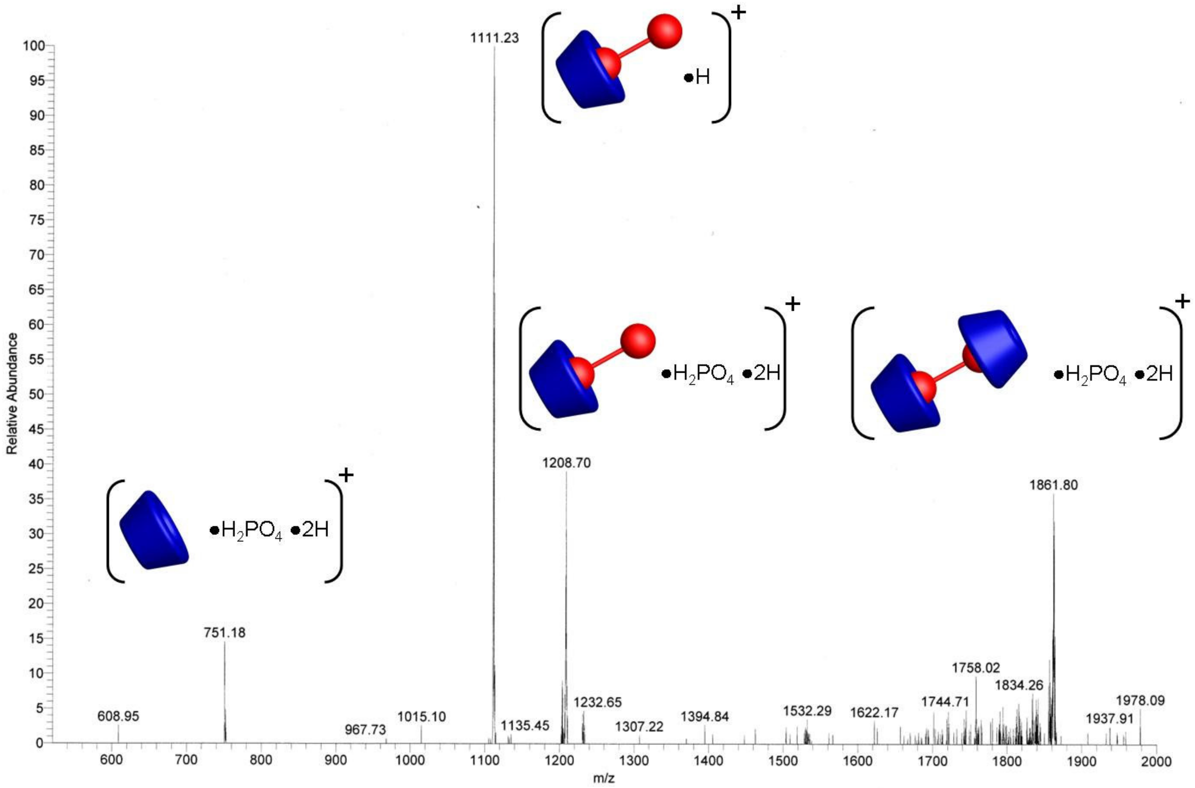


Figure S5. ESI-MS (positive) of **TAC4-BS** mixture.

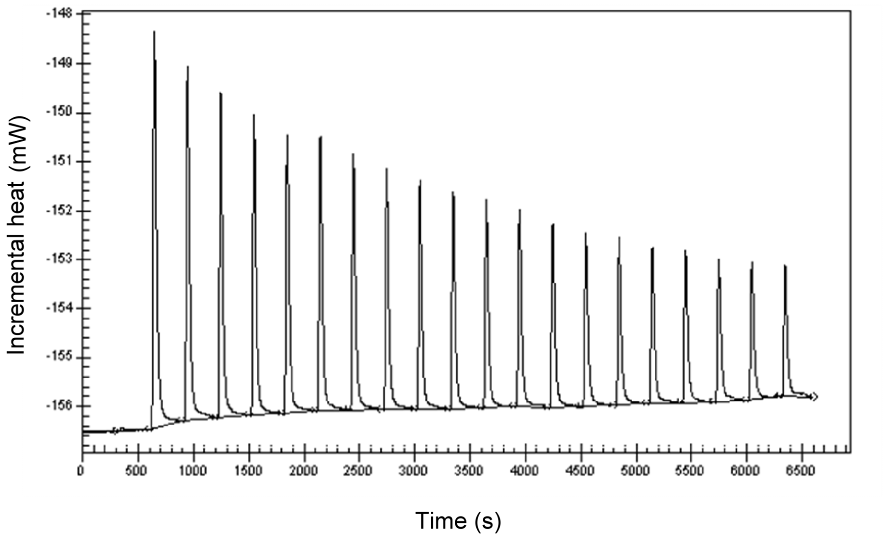


Figure S6. Calorimetric titration of **TAC4** (1.0×10^{-3} mol×dm^{-3}) with **BS** (2.9×10^{-3} mol×dm^{-3})

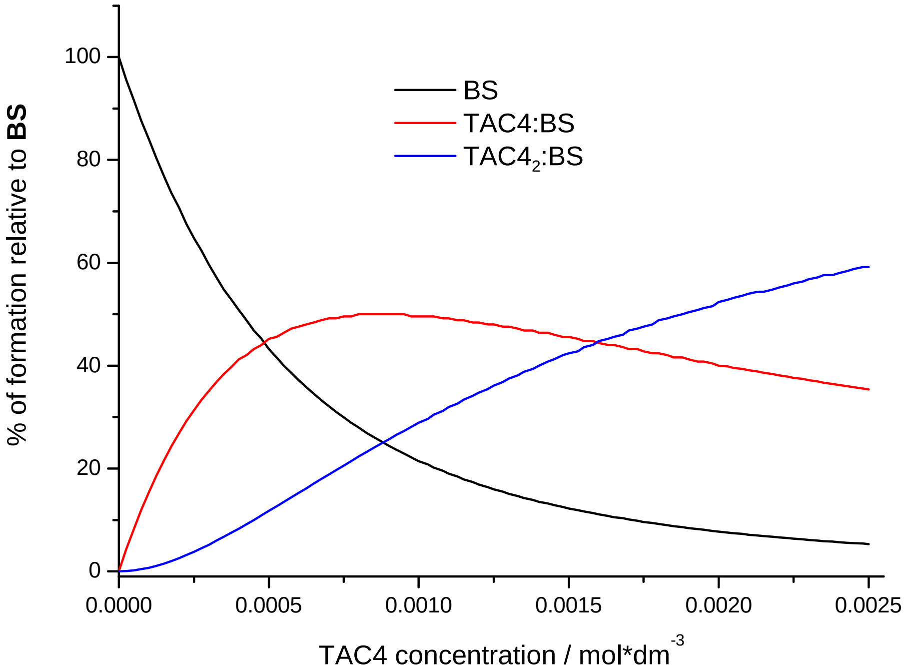


Figure S7. Species distribution

DOSY Experiments

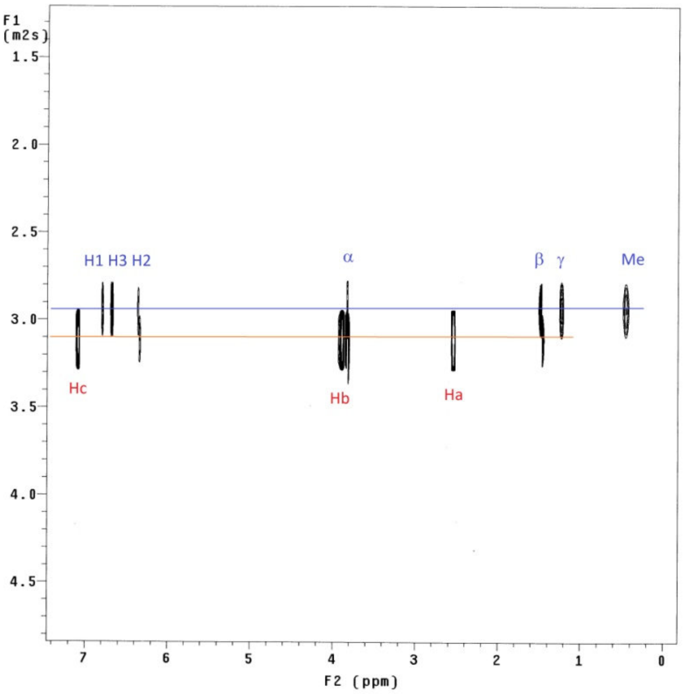


Figure S8. DOSY spectrum of a **TAC4/BS** mixture (H/G = 10).

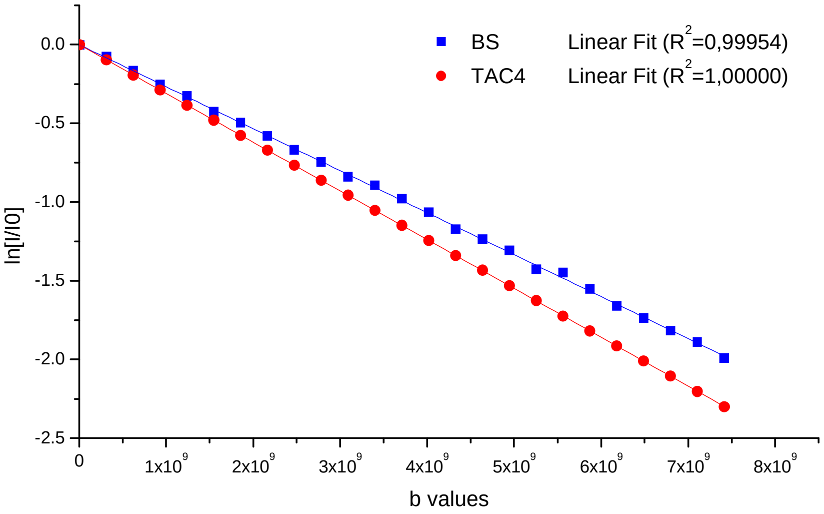


Figure S9. The natural log of the normalized signal attenuation (ln I/I_0) as a function of the b values for **TAC4** (●) and **BS** (■)

Since complexation is a dynamic process, assuming both the 1:1 and 2:1 stoichiometries and in the limit of the fast exchange, the measured diffusion coefficient, D^i_{exp}, for the host **TAC4** and the guest **BS** may be expressed as the sum of the contribution of the diffusion coefficient due to the free component, D^i_F, to the 1:1 complex, $D^i_{1:1}$, and to the 2:1 complex, $D^i_{2:1}$, each one weighted by its mole fraction that is:

$D^i_{exp} = \chi_F D^i_F + \chi_{1:1} D^i_{1:1} + n\, \chi_{2:1} D^i_{2:1}$ (eq. 1)

were χ_F, $\chi_{1:1}$ and $\chi_{2:1}$ refer to the molar fraction of the molecule whose chemical shifts are being observed and n is a stoichiometric factor (equal to 2 for **TAC4** and 1 for **BS**).[9] The mole fraction was derived from the binding constants obtained via ITC.

The dependency of the diffusion coefficient on the molecular weight[10] implies that, under identical condition, the following relations hold:

$D_{1:1}/D_{BS} = \sqrt[3]{(M_{BS}/M_{1:1})}$ (eq. 2)

$D_{2:1}/D_{BS} = \sqrt[3]{(M_{BS}/M_{2:1})}$ (eq. 3)

By introducing the D values, equation 1 can provide the curve expected for solutions containing HG only (n=0) or a mixture of HG+H_2G. The experimentally determined values lay on the curve generated by assuming the simultaneous formation of the HG and the H_2G.

	MW	**D_{calcd} ($\times 10^{-10}$ m^2 s^{-1})**	**$D_{extrapolated}$* ($\times 10^{-10}$ m^2 s^{-1})**
BS	456.7	3.8	3.80 (2)
C4TA:BS (1:1)	1112.5	2.8	2.94 (2)
C4TA$_2$:BS (2:1)	1768.3	2.4	2.39 (1)

*σ in parenthesis

ROESY Experiments

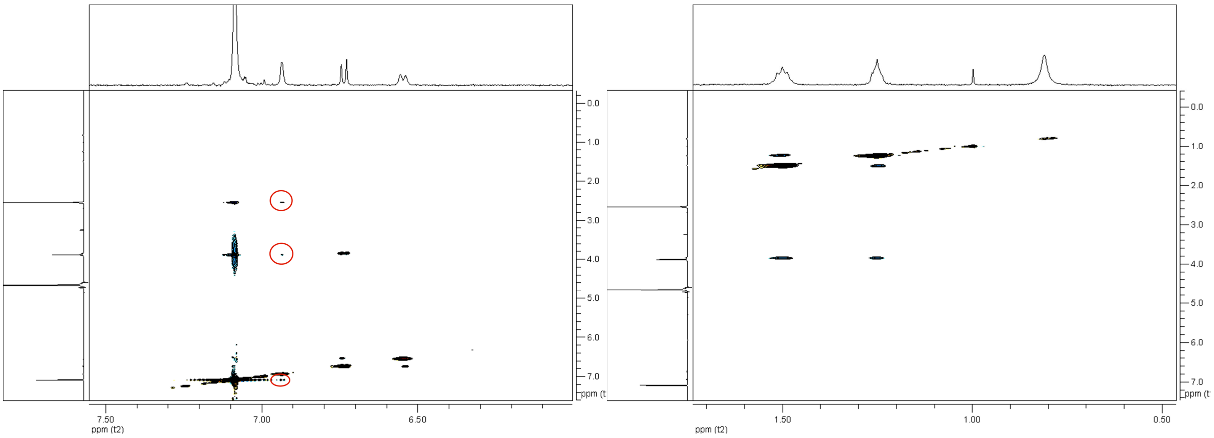
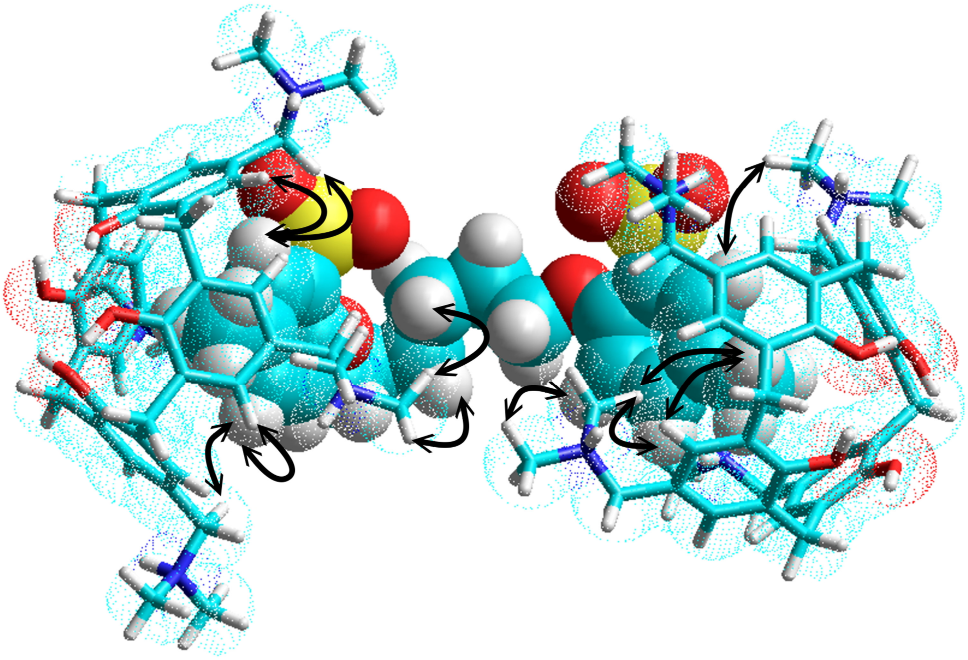


Figure S10. 2D ROESY interactions (phosphate buffer, D_2O, pD 6.8, **TAC4/BS** = 3.6).

Molecular modelling



Molecular modeling calculations were performed in two steps. In the first step, the initial structure and atomic charges of each single molecule were calculated by the PM6 method (Mopac 2007®). In the second step, the host, as well as the anion, were inserted into boxes containing 1000 water molecules and minimized (Molecular Mechanics, Amber force field; Hyperchem® 7.5). Finally, the anion was inserted between the two calixarene, and the resulting capsule inserted into a box containing 3800 water molecules and minimized (Polak-Ribiere, conjugate gradient; termination condition = 0.01 kcal Å^{-1} mol^{-1}).

References

1. C. D. Gutsche, K. C. Nam, *J. Am. Chem. Soc.*, 1988, **110**, 6153.
2. C. Sgarlata, C. Bonaccorso, F. G. Gulino, V. Zito, G. Arena, D. Sciotto, *New J. Chem*., 2009, **33**, 991.
3. ww.hyperquad.co.uk/hyss.htm.
4. http://www.mestrec.com.
5. http://www.hyperquad.co.uk/hypnmr.htm.
6. D. Wu, A. Chen, C. S. Johnson, Jr., *J. Magn. Reson*., 1995, **115A**, 260.
7. http://www.tainstruments.com.
8. P. Gans, A. Sabatini, A. Vacca, *J. Solution Chem.*, 2008, **37**, 467.

A. Guerrero-Martınez, G. Gonzalez-Gaitano, M. H. Vinas, G. Tardajos *J. Phys. Chem. B*, 2006**, 110**, 13819.

9. Y. Cohen, L. Avram, T. Evan-Salem, L. Frish, in *Analytical Methods in Supramolecular Chemistry*, ed. C. Schalley, Wiley-VCH Verlag, Weinheim, 2007, pp. 163-216.