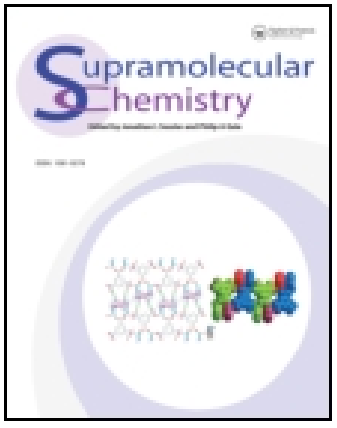


Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsch20

Gemini guests with spacers of various length drive the self-assembling of supramolecular capsules in water at neutral pH differently

Carmelo Sgarlata[a], Giuseppe Arena[a], Domenico Sciotto[a] & Carmela Bonaccorso[a]
[a] Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Viale A. Doria 6, 95125Catania, Italy
Published online: 25 Aug 2013.

To cite this article: Carmelo Sgarlata, Giuseppe Arena, Domenico Sciotto & Carmela Bonaccorso (2013) Gemini guests with spacers of various length drive the self-assembling of supramolecular capsules in water at neutral pH differently, Supramolecular Chemistry, 25:9-11, 696-702, DOI: 10.1080/10610278.2013.826806

To link to this article: http://dx.doi.org/10.1080/10610278.2013.826806

Supramolecular Chemistry, 2013
Vol. 25, Nos. 9–11, 696–702, http://dx.doi.org/10.1080/10610278.2013.826806

Gemini guests with spacers of various length drive the self-assembling of supramolecular capsules in water at neutral pH differently

Carmelo Sgarlata, Giuseppe Arena, Domenico Sciotto and Carmela Bonaccorso*

Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Viale A. Doria 6, 95125 Catania, Italy

(*Received 22 May 2013; final version received 10 July 2013*)

Water-soluble homodimeric capsules resulting from the electrostatic and hydrophobic interactions between a tetracationic calixarene receptor and gemini guests having the negatively charged ends separated by a $(—CH_2—)_n$ ($n = 2–6$) spacer are reported. The formation of the supramolecular capsules occurs through concerted hydrophobic and electrostatic interactions between the charged and aromatic groups of the guests and the host as indicated by ^{1}H NMR and DOSY NMR data. The different size of the guests may strongly affect the stability of the capsule. The surprising features of these host–guest systems disclose new paths for the design of more efficient anion-templated capsules in highly competitive media such as water.

Keywords: calixarenes; gemini guest; supramolecular capsules; water chemistry; self-assembly

1. Introduction

The comprehension of the molecular properties of entities that are confined in small spaces is of crucial interest in chemistry, since confined molecules have properties that may be quite different from those of molecules that move freely in solution (*1*). Considerable efforts have been devoted to the synthesis of molecular containers possessing a confined environment that may stabilise reactive intermediates (*2*) or may catalyse reactions (*3*). Self-assembled nanocapsules are containers obtained through the rational design of the molecular scaffold as well as of the building block (*4*).

Non-covalent, weak interactions have been widely exploited to drive the assembly of molecules into nanometre-sized supramolecular structures in solution (*5*). In organic media, a variety of strategies have been used to build molecular containers that assemble through non-covalent interactions, such as hydrogen bonds (*6*) or metal–ligand interactions (*7*). On the other hand, the design of water-compatible dynamic non-covalent containers is a great challenge, and methods to obtain an active control on the encapsulation or transport of drugs or other relevant molecules are topics of interest.

Anionic components able to drive the self-assembly of molecules have been recently used in supramolecular chemistry to obtain non-covalently linked molecular architectures (*8*). Molecular capsules may find applications in the (a) removal and extraction of toxic species, (b) drug delivery and (c) molecular catalysis.

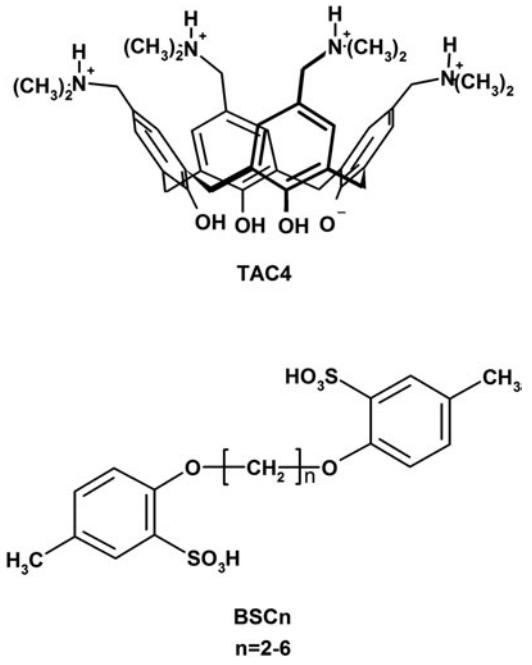
With the aim of building up supramolecular anion receptors by using simple building blocks, we resorted to the positively charged calix[4]arene host **TAC4** (Scheme 1), which has been successfully used for both the recognition of organic anions and the formation of homodimeric capsules in water (*9*, *10*). We have recently shown that a gemini guest, having both aromatic units and negative charges, triggers the self-assembling of a homodimeric capsule in the presence of **TAC4** in aqueous solution. We also found that the inclusion process is due to concerted electrostatic, CH–π and π–π interactions between the guest and host functional groups, as well as to the spatial arrangement of the host scaffold (*9*).

Although host–guest interactions play a significant role in capsule formation, they are not the only relevant factors, as guest size and shape may largely affect the assembly of the supramolecular structure. We have designed anionic gemini guests of variable size (**BSCn**, $n = 2–6$, Scheme 1) to explore their ability to act as templating agents for the self-assembling of capsules. Here, we report on supramolecular entities resulting from the interaction of these guests with **TAC4** in neutral aqueous solution and show that they may form capsules the stability of which depends on the length of the $(—CH_2—)_n$ (where $n = 2–6$) spacer.

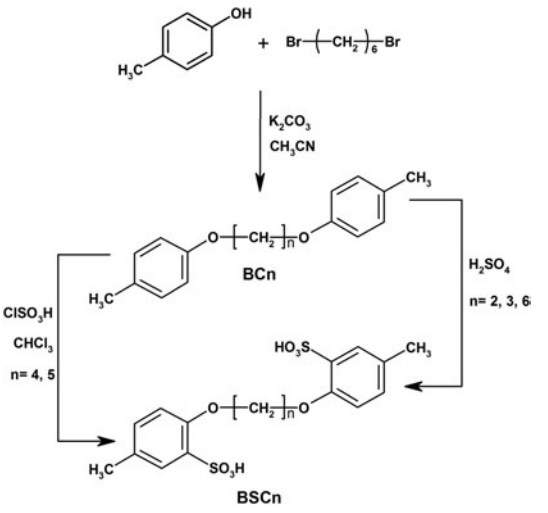
2. Results and discussion

The dianionic guests **BSCn** ($n = 3–5$) were synthesised by following the two-step procedure reported in Scheme 1, while **BSC2** and **BSC6** were synthesised as reported previously (*10*). 4-Methyl-phenol was first alkylated with terminal dibromoalkanes of variable length, then the BCn phenylethers were sulphonated with H_2SO_4 (when n is 2, 3

*Corresponding author. Email: bonaccorsoc@gmail.com



Scheme 1. The investigated host and guest.



Scheme 2. Synthesis of the **BSCn** guests.

and 6) or with $ClSO_3H$ (for $n = 4$ and 5). All the intermediates and final compounds were characterised by ^1H and ^{13}C NMR spectroscopies and ESI mass spectrometry (see Supplementary Information, available online) (Scheme 2).

Standard ^1H NMR titrations (*11*) were carried out to determine both the stereochemistry of inclusion and the binding affinities of **BSCn** ($n = 3–5$) for **TAC4** in water at neutral pH. Due to the fast exchange between the free and the complexed species on the NMR timescale, the guest signals were detected as single resonances. When the host concentration increases, all the guest signals shift upfield and the complexation-induced shifts (CIS) follow the order Me > ArH ≫ CH_2 (Figure 1). The trend reported in Figure 1 has already been observed for the analogous **BSC2–TAC4** and **BSC6–TAC4** systems (*10*).

The selective inclusion of the aromatic moiety of the guest is supported by the large upfield shift of both the signals of the methyl groups and the two neighbouring aromatic protons, indicating that the above groups are included into the host cavity and experience the magnetic shielding of the aromatic rings of **TAC4**. Such an arrangement maximises the CH–π and π–π interactions between the host and the guest and somewhat keeps the lipophilic moieties of **BSCn** away from the polar aqueous environment. Negligible shifts are observed for the other guest signals suggesting that the sulphonate groups are located near the portal of the host, to take full advantage of the electrostatic interactions with the ammonium groups at the upper rim of the calixarene, while the alkyl chains are located outside the cavity.

TAC4 self-assembles to give capsular structures in which the included guest is reversibly bound to the host; moreover, the ad hoc tailored functionalisation of both the calixarenic cavity and **BSCn** allows for the control of the orientation and location of encapsulated guests.

The refinement of the NMR titration data yields the binding constants for the different **BSCn–TAC4** systems in buffered D_2O (pD 7.1) at 27°C (*12*). A good fit of the experimental data was obtained only by considering the simultaneous formation of complex species having both 1:1 and 2:1 host–guest stoichiometry. The association constants ($\log \beta$) for these species, the host–guest equilibria and the distribution diagrams are shown in Table 1 and Figures 2 and 3, respectively.

The species distribution diagrams indicate that **BSC4** forms a supramolecular capsule (i.e. both HG and H_2G species are successfully refined) with a stability comparable to that observed for **BSC2** and **BSC6** (*10*) while **BSC5** assembles into a less stable capsular entity. Surprisingly, **BSC3** seems poorly suitable for capsule formation; the HG species is by far the most relevant in this system.

The formation of the homodimeric structure does not imply any stabilising linkage between the two calixarenic scaffolds; concerted electrostatic and hydrophobic interactions between **TAC4** and the guests are the attractive forces holding together the supramolecular assemblies. However, the different length and number of methylene groups on the alkyl chain of the guests seem to affect the efficiency of the capsule templation process.

The assemblies with an odd number of CH_2 units are less stable than **BSC4**, probably owing to an unsuitable arrangement of the two calixarenic scaffolds around **BSC3**

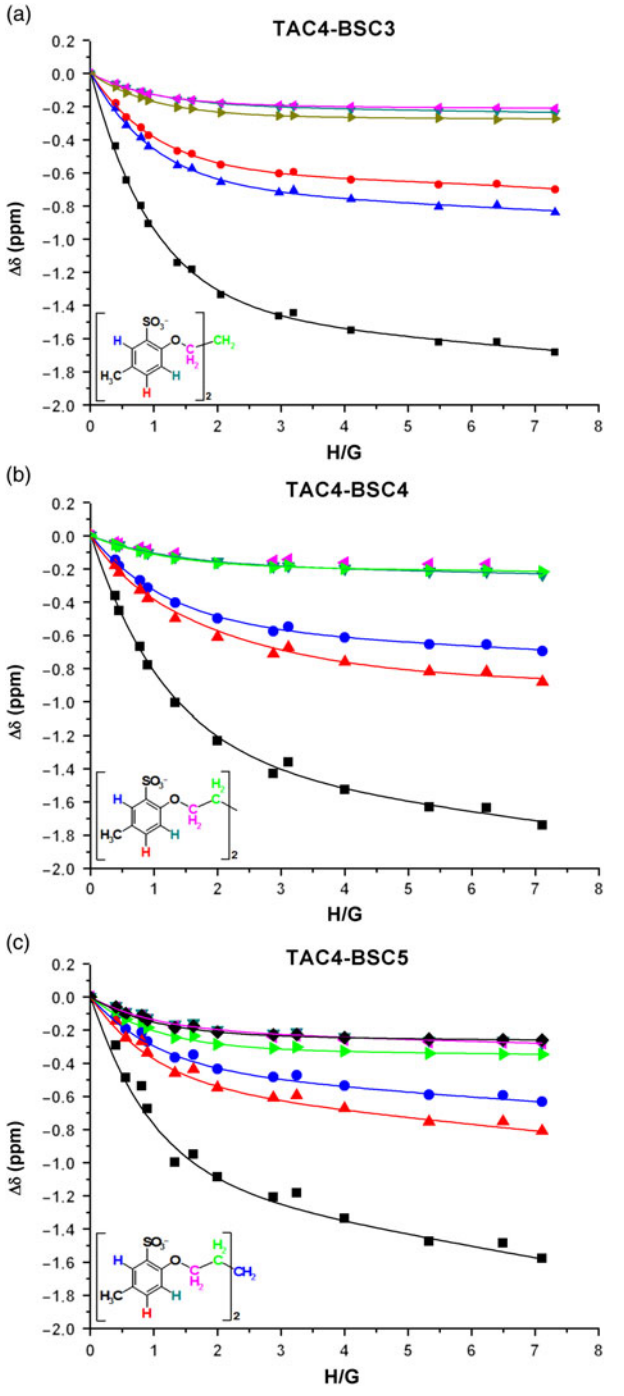


Figure 1. (Colour online) CIS diagrams for the **BSCn**–**TAC4** systems ($n = 3, 4, 5$ for (a), (b) and (c), respectively) in D_2O, pD 7.1, 27°C. $C_{\mathbf{BSCn}} = 2.5 \times 10^{-4}$ mol dm^{-3}.

(Figure 4). Probably, the alkyl chain conformation and its low degree of conformational freedom keep the second negative charge of **BSC3** at longer distance from the upper rim of the host, which would determine the slightly lower value observed also for the first equilibrium. The relatively longer and more flexible **BSC5** alkylic chain partially accounts for the larger stability of the structure with the longer spacer

Table 1. Binding constants ($\log \beta$)[a] for the **BSCn**–**TAC4** systems ($n = 2$–6) in D_2O at pD 7.1, 27°C.

Guest	$\log \beta_1$	$\log \beta_2$
BSC2[b]	4.54	7.85
BSC3	4.22 (1)	6.43 (2)
BSC4	4.52 (3)	7.69 (3)
BSC5	4.45 (3)	7.20 (3)
BSC6[c]	4.34	7.40

[a] σ in parentheses.
[b] From Ref. (*10b*).
[c] From Ref. (*10a*).

(7.20 vs. 6.43), though the **BSC5** assembly is less stable than those formed by the **BSCn** ($n = 2, 4, 6$) homologues.

Diffusion-ordered NMR spectroscopy (DOSY) provides further evidence that supports the unexpected behaviour of the **BSC3**–**TAC4** system. As the free and bound guest exchange fast on the NMR timescale, the observed diffusion coefficients are the weighted average of the values of the free and bound guest. The addition of increasing amounts of **TAC4** affects the motion of **BSC3** while it causes a small effect on the **TAC4** diffusion coefficient (Figure 5); the guest diffuses more slowly than in its free form, which is consistent with an increase of its effective size due to host–guest interactions (*13*).

Only the model (HG + H_2G) nicely fits the experimental self-diffusion coefficients, thus pointing out that the two species coexist in neutral solution. However, both NMR titration and DOSY data indicate that the amount of $(\mathbf{TAC4})_2$–**BSC3** assembly forming in solution is relatively small (< 30%, Figure 3(a)) even in the presence of a large excess of **TAC4** (Figure 5). Most of the experimental diffusion coefficients values lie above the value expected for 1:1 species (blue line), supporting that HG is the main species in solution.

The diffusion coefficients extrapolated from the experimental data (D_{extr}, Table 2) for the HG and H_2G complexes (3.05×10^{-10} m^2 s^{-1} and 2.52×10^{-10} m^2 s^{-1}, respectively) are lower than those of the free components ($D_{TAC4} = 3.10 \times 10^{-10}$ m^2 s^{-1}, $D_{BSC3} = 4.04 \times 10^{-10}$ m^2 s^{-1}) and nicely match the theoretical values (D_{calcd}).

The diffusion coefficient extrapolated for $(\mathbf{TAC4})_2$–**BSC3** is somewhat comparable to that of the capsule formed by **BSC2** (*10b*) and is significantly larger than that formed by **BSC6** (*10a*), which corroborates the compact capsular assembly. These findings support the formation of the self-assembled structure involving **BSC3**, although the amount of capsule is the lowest observed for the series of guests reported here.

3. Conclusions

Dianionic gemini guests having different size can be successfully used as templating agents for the assembly of nanoscale homodimeric capsules in aqueous solution at

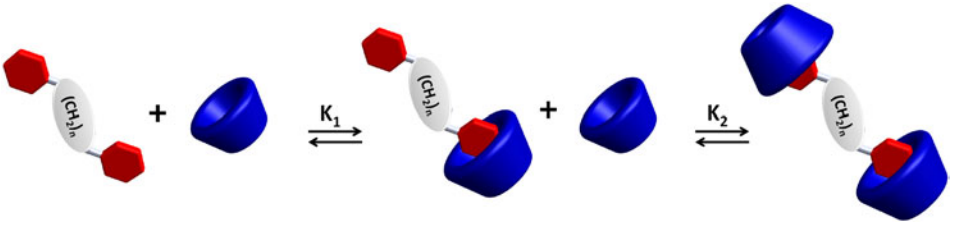


Figure 2. (Colour online) Schematic of the host–guest equilibria for the **TAC4**–**BSCn** systems.

neutral pH. Capsules are formed by concerted hydrophobic and electrostatic interactions between the aromatic and charged moieties at both ends of the **BSCn** guests and the tetracationic calix[4]arene host.

DOSY experiments and the accurate determination of the species existing in solution reveal that the amount of dimeric capsule that forms strongly depends on the number of methylene groups on the alkyl chain of the guest. This paves the way to new strategies for the design of more efficient supramolecular containers that could be used as molecular reactors or shuttles for the delivery of biologically relevant molecules. Isothermal titration calorimetry measurements and theoretical calculations are currently underway to single out the forces that drive the capsule formation processes.

4. Experimental

4.1 General

TAC4 was obtained according to the procedure described by Gutsche et al. (*14*). The concentration of **BSCn** and **TAC4** was obtained by correcting for the water content determined via TGA. All the chemicals were obtained from Sigma Aldrich (St. Louis, MO, USA) and used as received, after drying. Thin layer chromatography was carried out on silica gel plates (Merck 60, F254, Merck, Darmstadt, Germany). All reactions were carried out under nitrogen atmosphere unless otherwise stated. High-purity water (Millipore, Milli-Q Element A 10 ultrapure water, Billerica, MA, USA) and A-grade glassware were used throughout. The distribution diagram and the mole fraction values were obtained with HySS (*15*).

4.2 NMR experiments

NMR experiments were carried out at 27°C using a 500 MHz spectrometer (^{1}H NMR at 499.88 MHz, ^{13}C NMR 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.

NMR titrations were carried out by mixing **BSCn** and **TAC4** in the appropriate ratios in NMR tubes in D_2O (**BSCn** concentration was kept constant at 2.5×10^{-4} moldm^{-3}; phosphate buffer 2.5×10^{-2} mol dm^{-3}). The chemical shifts corresponding to all **BSCn** resonances collected in the 1–8 host–guest range were simultaneously fit using HyperNMR (*12*); the above ratio ensured that the amount of complex formed ranged from 20% to 80% of the total guest concentration.

NMR diffusion measurements were carried out using the bipolar-pulsed gradient-stimulated echo (due to the long eddy-current delay) Varian pulse sequences (*16*) 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 constant concentration of **BSCn** (0.25 mmol dm^{-3}) was used while the concentration of **TAC4** ranged from 0.25 to 2.50 mmol dm^{-3}.

The diffusion coefficients were obtained by the following equation:

$$\ln\left(\frac{I}{I_0}\right) = -\gamma^2\delta^2G^2\left(\frac{2}{\pi}\right)^2\left(\frac{\Delta-\delta}{4}\right)D = -b\,D,$$

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.

4.3 Synthesis

4.3.1 General procedure for the synthesis of BCn

Terminal dibromoalkane (5.0 mmol) was added to a stirred suspension of 4-methyl-phenol (1.04 ml, 10.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) in acetonitrile (50 ml). The mixture was refluxed overnight and then allowed to cool

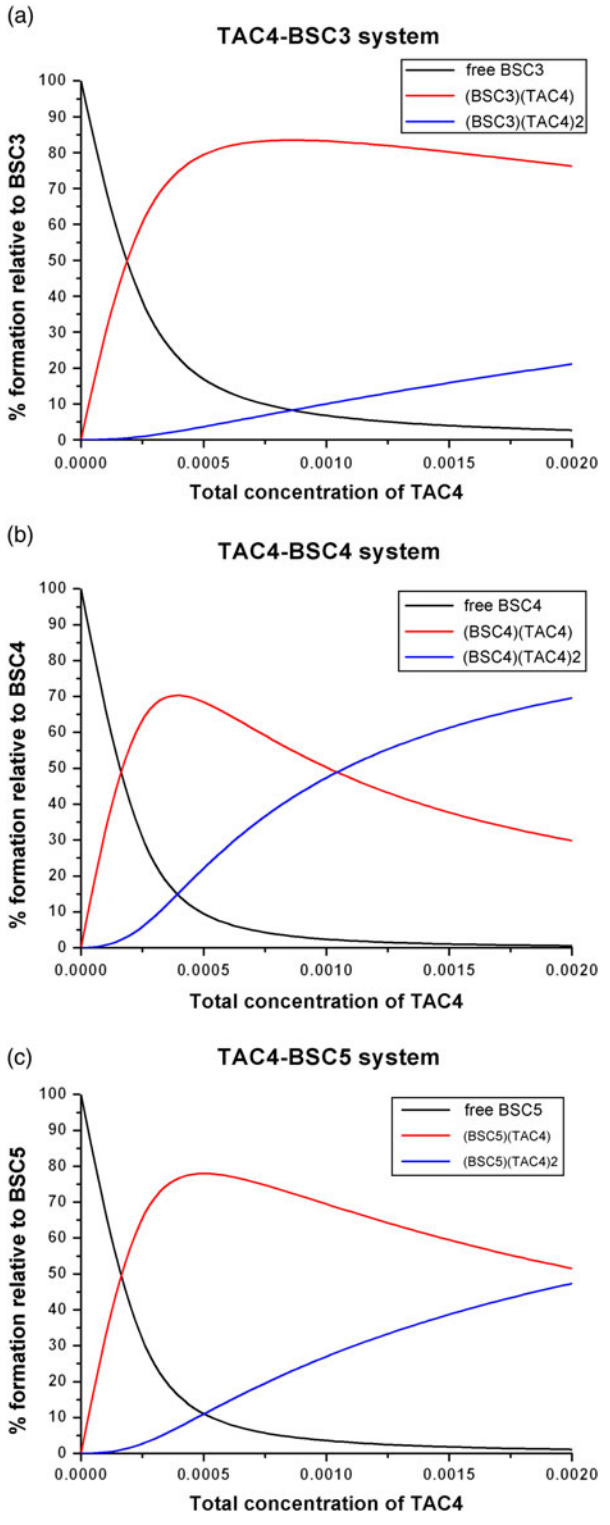


Figure 3. (Colour online) Species distribution diagrams for the **TAC4–BSCn** systems ($n = 3$, 4 and 5 for (a), (b) and (c) respectively). $C_{\mathbf{BSCn}} = 2.5 \times 10^{-4}$ mol dm^{-3}.

down to room temperature (r.t.). After solvent removal, the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was evaporated to dryness and the

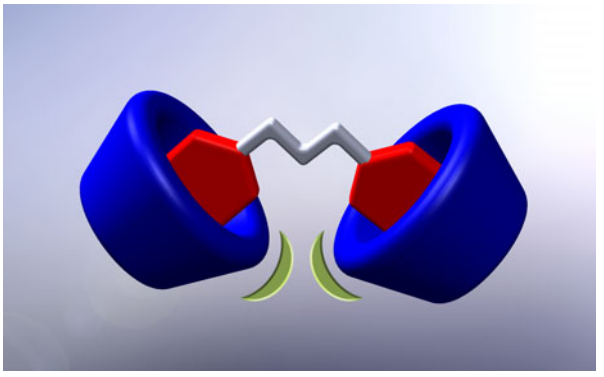


Figure 4. (Colour online) Schematic of the **(TAC4)$_2$–BSC3** assembly.

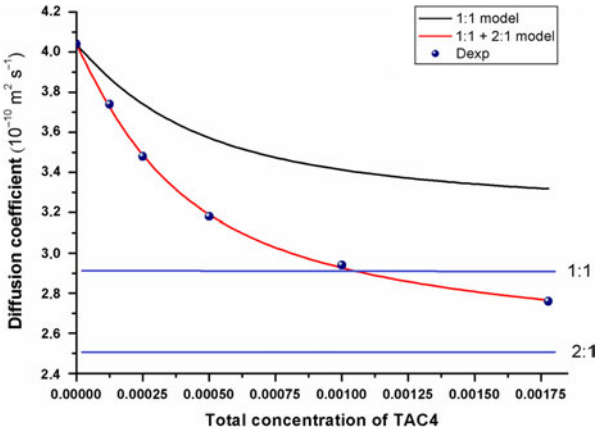


Figure 5. (Colour online) **BSC3** self-diffusion coefficients in D_2O at pD 7.1, 27°C. Blue full circles; experimental data points; black line; curve predicted for the HG model; red line; curve predicted for the HG + H_2G model. Blue lines indicate the expected diffusion value for HG and H_2G, respectively. $C_{\mathbf{BSCn}} = 2.5 \times 10^{-4}$ mol dm^{-3}.

resulting precipitate was purified by re-crystallisation from methanol.

BC3: (Yield 84%) NMR: δ_H (500 MHz, $CDCl_3$, 27°C) 7.08 (d, ^3J(H,H) = 8.6 Hz, 4H; ArH); 6.82 (d, ^3J(H,H) = 8.6 Hz, 4H; ArH); 4.14 (t, ^3J(H,H) = 6.1 Hz, 4H; OCH_2); 2.29 (s, 6H; CH_3); 2.24 (m, 2H; CH_2); δ_C (125 MHz, $CDCl_3$, 27°C) 156.76, 129.89, 129.85, 114.39, 64.61, 29.42, 20.44 ppm. ESI-MS *m/z*: 279.23 (100%) [$M + Na^+$].

BC4: (Yield 81%) NMR: δ_H (500 MHz, $CDCl_3$, 27°C) 7.08 (d, ^3J(H,H) = 8.5 Hz, 4H; ArH); 6.81 (d, ^3J(H,H) = 8.5 Hz, 4H; ArH); 4.01 (m, 4H; OCH_2); 2.30 (s, 6H; CH_3); 1.97 (m, 4H; CH_2); δ_C (125 MHz, $CDCl_3$, 27°C) 156.86, 129.85, 129.78, 114.37, 67.54, 26.06, 20.44 ppm. ESI-MS *m/z*: 293.27 (100%) [$M + Na^+$].

BC5: (Yield 93%) NMR: δ_H (500 MHz, $CDCl_3$, 27°C) 7.10 (d, ^3J(H,H) = 8.7 Hz, 4H; ArH); 6.83 (d, ^3J(H,H) = 8.7 Hz, 4H; ArH); 3.98 (t, ^3J(H,H) = 6.6 Hz, 4H; OCH_2); 2.31 (s, 6H; ArH); 1.87 (m, 2H; CH_2); 1.77 (m, 2H; CH_2); δ_C (125 MHz, $CDCl_3$, 27°C) 156.94, 129.86,

Table 2. Self-diffusion coefficients for the **BSC3–TAC4** system in D_2O at pD 7.1, 27°C.

	MW	D_{calcd} ($\times 10^{-10}\,m^2\,s^{-1}$)	D_{extr}[a] ($\times 10^{-10}\,m^2\,s^{-1}$)
BSC3	414	4.04	4.04 (2)
TAC4	656	3.10	3.10 (1)
TAC4:BSC3 (1:1)	1070	2.92	3.05 (2)
$TAC4_2$:BSC3 (2:1)	1726	2.51	2.52 (2)

[a] σ in parentheses.

129.73, 114.40, 67.85, 29.12, 22.75, 20.46 ppm. ESI-MS *m/z*: 307.30 (100%) $[M + Na^+]$.

4.3.2 *General procedure for the synthesis of BSCn*

4.3.2.1 Method A. **BCn** (4.0 mmol) was added to 2.5 ml of H_2SO_4 (96%) kept at 0°C. The suspension was stirred at r.t. for 0.5 h. The solvent was removed by vacuum filtration, and the residue was washed with ethyl acetate. The orange solid was purified by re-crystallisation from methanol.

BSC3: (Yield 86%) NMR: δ_H (500 MHz, $CDCl_3$, 27°C) 7.46 (s, 2H; ArH); 7.18 (d, 2H; ArH); 6.90 (d, 2H; ArH); 3.99 (t, 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, $CDCl_3$, 27°C) 153.36, 133.55, 129.95, 129.65, 128.28, 113.64, 65.25, 28.40, 19.41 ppm ESI-MS *m/z*: 208.17 (100%) $[M^{2-}]$.

4.3.2.2 Method B. **BCn** (2 mmol) was solubilised in anhydrous $CHCl_3$ (5 ml) at r.t. and then chlorosulphonic acid (0.31 ml) was added slowly. The mixture was stirred at r.t. overnight and the solid was filtered off under vacuum. The residue was solubilised with water (6 ml) and washed three times with $CHCl_3$ (4 ml). HCl 37% was then added to the aqueous phase; the resulting precipitate was removed by vacuum filtration and purified by re-crystallisation from ethanol.

BSC4 (Yield 46%) NMR: δ_H (500 MHz, D_2O, 27°C): 7.49 (d, ^3J(H,H) = 2.2 Hz, 2H; ArH); 7.23 (dd, ^3J(H,H) = 2.2 Hz, ^3J(H,H) = 8.5 Hz, 2H; ArH); 6.96 (d, ^3J(H,H) = 8.5 Hz, 2H; ArH); 4.10 (m, 4H; OCH_2); 2.20 (s, 6H; CH_3); 1.92 (m, 4H; CH_2); δ_C (125 MHz, $CDCl_3$, 27°C) 153.41, 133.53, 129.85, 129.71, 128.35, 113.74, 68.46, 24.91, 19.43 ppm. ESI-MS *m/z*: 217.19 (100%) $[M^{2-}]$.

BSC5 (Yield 54%) NMR: δ_H (500 MHz, D_2O, 27°C): 7.50 (s, 2H; ArH); 7.23 (d, 2H; ArH); 6.95 (d, 2H; ArH); 4.04 (t, 4H; OCH_2) 2.19 (s, 6H; ArH) 1.78 (m, 4H; CH_2) 1.55 ppm (m, 4H; CH_2); δ_C (125 MHz, $CDCl_3$, 27°C) 153.51, 133.52, 129.87, 129.79, 128.36, 113.79, 68.88, 27.88, 21.48, 19.42 ppm ESI-MS *m/z*: 221.22 (100%) $[M^{2-}]$.

Supporting Information

Supplementary information (available online): ^1H and ^{13}C NMR spectra of BCn and BSCn.

Acknowledgements

University of Catania (Progetto d'Ateneo) and MIUR (Firb MERIT RBNE08HWLZ) are gratefully thanked for partial support.

References

(1) (a) Koblenz, T.S.; Wassenaar, J.; Reek, J.N.H. *Chem. Soc. Rev.* **2008**, *37,* 247–262. (b) Breiner, B., Clegg, J.K.; Nitschke, J.R. *Chem. Sci.* **2011**, *2,* 51–56. (c) Amouri, H; Desmarets, C.; Moussa, J. *Chem. Rev.* **2012**, *112,* 2015–2041. (d) Ajami, D.; Rebek, J., Jr. *Acc. Chem. Res.* **2013**, *46,* 990–999. (e) Ward, M.D.; Raithby, P.R. *Chem. Soc. Rev.* **2013**, *42,* 1619–1636.

(2) (a) Cram, D.J.; Tanner, M.E.; Thomas, R. *Angew. Chem. Int. Ed. Engl.* **1991**, *30,* 1024–1027. (b) Warmuth, R. *Chem. Commun.* **1998**, 59–60. (c) Arena, G.; Contino, A.; Magri, A.; Sciotto, D.; Lamb, J.D. *Supramol. Chem.* **1998**, *10,* 5–15. (d) Ziegler, M.; Brumaghim, J.L.; Raymond, K.N. *Angew. Chem. Int. Ed.* **2000**, *39,* 4119–4121. (e) Körner, S. K.; Tucci, F.C.; Rudkevich, D.M.; Heinz, T. *Chem. Eur. J.* **2000**, *6,* 187–195. (f) Chen, J.; Körner, S.; Craig, S.L.; Rudkevich, D.M.; Rebek, J., Jr. *Nature* **2002**, *415,* 385–386. (g) P. Mal, B. Breiner, K. Rissanen, J.R. Nitschke, Science **2009**, *324,* 1697–1699. (h) Gao, C.-Y.; Zhao, L.; Wang, M.-X. *J. Am. Chem. Soc.* **2012**, *134,* 824–827.

(3) (a) Kusukawa, T.; Yoshizawa, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2001**, *40,* 1879–1884. (b) Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M. *J. Am. Chem.Soc.* **2003**, *125,* 3243–3247. (c) Fiedler, D.; Bergman, R.G.; Raymond, K.N. *Angew. Chem. Int. Ed.* **2004**, *43,* 6748–6751. (d) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312,* 251–254. (e) Yoshizawa, M.; Klosterman, J.K.; Fujita, M. *Angew. Chem. Int. Ed.* **2009**, *48,* 3418–3438. (f) Dong, Z.; Luo, Q.; Liu, J. *Chem. Soc. Rev.* **2012**, *41,* 7890–7908. (g) Ronson, T.K.; Zarra, S.; Black,S.P.; Nitschke, J.R. *Chem. Commun.* **2013**, *49,* 2476–2490.

(4) (a) Hof, F.; Craig, S.L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41,* 1488–1508. (b) Russel-Seidel, S.; Stang, P.J. *Acc. Chem. Res.* **2002**, *35,* 972–983. (c) Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38,* 369–378. (d) Dalgarno, S.J.; Power, N.P.; Atwood, J.L. *Coord. Chem. Rev.* **2008**, *252,* 825–841. (e) Laughrey, Z.; Gibb, B.C. *Chem. Soc. Rev.* **2011**, *40,* 363–386. (f) Ariga,K.; Ito, H.; Hill, J.P.; Tsukube, H. *Chem. Soc. Rev.* **2012**, *41,* 5800–5835. (g) Yamanaka, M.; Kobayashi, K. *Asian J. Org. Chem.* **2013**, *2,* 276–289.

(5) (a) Leininger, S.; Olenyuk, B.; Stang, P.J. *Chem. Rev.* **2000**, *100,* 853–908. (b) Prins, L.J.; Reinhoudt, D.N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40,* 2382–2426. (c) Greig, L.M.; Philp, D. *Chem. Soc. Rev.* **2001**, *30,* 287–302.

(6) (a) Rebek, J., Jr. *Chem. Commun.* **2000**, 637–643. (b) Rincón, A.M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **2001**, *123,* 3493–3498. (c) Kobayashi, K.; Ishii, I.; Sakamoto, S.; Shirasake, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125,* 10615–10624. (d) Kerchoffs, J.M.C.A.; van Leeuven, F.W.R.; Spek, A.L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D.N. *Angew. Chem., Int. Ed.* **2003**, *42,* 5717–5722. (e) Sansone, F.;

Baldini, L.; Casnati, A.; Chierici, E.; Faimani, G.; Ugozzoli, F.; Ungaro, R. *J. Am. Chem. Soc.* **2004**, *126,* 6205–6206. (f) Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2005**, *44,* 2068–2078. (g) Vriezema, D.M.; Comellas Aragonés, M.; Elemans, J.A.A.W.; Cornelissen, J.J.L.M.; Rowan, A.E.;. Nolte, R.J.M. *Chem. Rev.* **2005**, *105,* 1445–1489. (h) Dalgarno, S.J.; Thallapally, P.K.; Barbour, L.J.; Atwood, J.L. *Chem. Soc. Rev.* **2007**, *36,* 236–245. (i) Davis, J.T.; Spada, G.P. *Chem. Soc. Rev.* **2007**, *36,* 296–313. (l) Adriaenssens, L.; Ballester, P. *Chem. Soc. Rev.* **2013**, *42,* 3261–2377.

(7) (a) Fox, O.D.; Leung, J.F.Y.; Hunter, J.M.; Dalley, N.K.; Harrison, R.G. *Inorg. Chem.* **2000**, *39,* 783–790. (b) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509–518. (c) Radhakrishnan, U.; Schweiger, M.; Stang, P.J. *Org. Lett.* **2001**, *3,* 3141–3143. (d) Lehn, J.-M. *Science* **2002**, *295,* 2400–2403. (e) Kryschenko, Y.K.; Seidel, S.R.; Muddiman, D.C.; Nepomuceno, A.I.; Stang, P.J. *J. Am. Chem. Soc.* **2003**, *125,* 9647–9652. (f) Leung, D.H.; Fiedler, D.; Bergman, R.G.; Raymond, K.N. *Angew. Chem., Int. Ed.* **2004**, *43,* 963–966. (g) Fiedler, D.; Leung, D.H.; Bergman, R.G.; Raymond, K.N. *Acc. Chem. Res.* **2005**, *38,* 351–360. (h) Nitschke, J.R. *Acc. Chem. Res.* **2007**, *40,* 103–112.

(8) (a) Bianchi, A.; Bowman-James,K.; García-España, E. *Supramolecular Chemistry of Anions*, Wiley-VCH: New York, 1997. (b) Gale, P.A. *Coord. Chem. Rev.* **2001**, 213, 79–128. (c) Beer, P.D.; Gale, P.A. *Angew. Chem., Int. Ed.* **2001**, *40,* 486–516. (d) Sessler, J.L.; Gale, P.A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, 2006. (e) Gale, P.A.; Gunnalaugsson,T. *Chem. Soc. Rev.* **2010**, *39,* 3595–3596. (f) Steed, J.W. *Chem. Soc. Rev.*, **2010**, 39, 3686–3699. (g) Amendola, V.; Fabbrizzi, L.; Mosca, L. *Chem. Soc. Rev.* **2010**, *39,* 3889–3915. (h) Arunachalam, M.; Ghosh, P. *Chem. Commun.* **2011**, *47,* 8477–8492. (i) Gale, P.A., *Chem. Commun.* **2011**, *47,* 82–86. (l) Chifotides, H.T.; Dunbar, Kim, R. *Acc. Chem. Res.* **2013**, *46,* 894–906.

(9) (a) Sgarlata, C.; Bonaccorso, C.; Gulino, F.G.; Zito, V.; Arena, G.; Sciotto, D. *New J. Chem.* **2009**, *33,* 991–997. (b) Sgarlata, C.; Bonaccorso, C.; Gulino, F.G.; Zito, V.; Arena, G.; Sciotto, D. *Tetrahedron Lett.* **2009**, *50,* 1610–1613. (c) Bonaccorso, C.; Ciadamidaro, A.; Zito, V.; Sgarlata, C.; Sciotto, D.; Arena, G. *Thermochim. Acta* **2012**, *530,* 107–115.

(10) (a) Bonaccorso, C.; Ciadamidaro, A.; Sgarlata, C.; Sciotto, D.; Arena, G., *Chem. Commun.* **2010**, *46,* 7139–7141. (b) Bonaccorso, C.; Sgarlata, C.; Grasso, G.; Zito,V.; Sciotto, D.; Arena, G.; *Chem. Commun.* **2011**, *47,* 6117–6119.

(11) Fielding, L. *Tetrahedron* **2000**, *56*, 6151–6170.

(12) Frassineti, C; Alderighi, L.; Gans, P.; Sabatini, A.; Vacca, A.; Ghelli, S.; *Anal. Bioanal. Chem*. **2003**, *376*, 1041–1052.

(13) Cohen, Y.; Avram, L.; Evan-Salem, T.; Frish, L. In Diffusion NMR in supramolecular chemistry and complexed systems. *Analytical Methods in Supramolecular Chemistry*; Schalley, C., Ed.; Wiley-VCH Verlag: Weinheim, 2007; pp 163–216.

(14) Gutsche, C.D.; Nam, K.C. *J. Am. Chem. Soc.* **1988**, *110*, 6153–6162.

(15) Alderighi, L.; Gans, P.; Ienco, A.; Peters, D.; Sabatini, A.; Vacca, A.; *Coord. Chem. Rev.* **1999**, *184*, 311–318.

(16) Wu, D.; Chen, A.; Johnson, Jr., C.S. *J. Magn. Reson.* **1995**, *115A*, 260–264.