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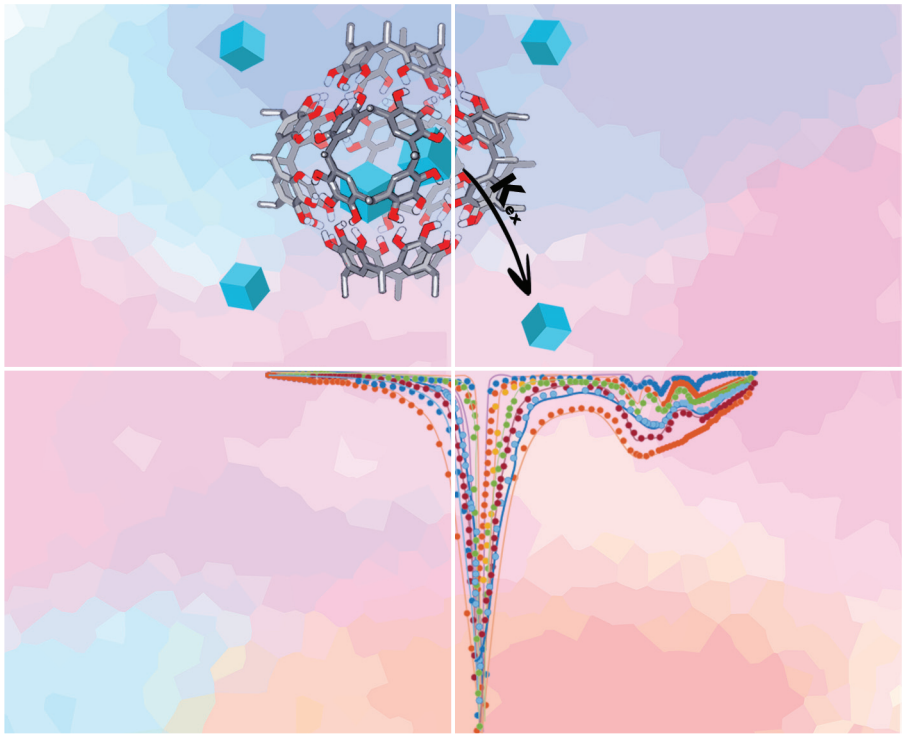

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Advanced ^{19}F-NMR studies shed new light on encapsulation of isosteric guests in the hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes†

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The hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes are fascinating, catalytically active, and highly accessible structures having large cavities. Despite the apparent similarity between these two types of hexamers, the hexameric capsules of C_{11}-resorcin[4]arenes (**1**) are much more efficient nanoreactors than the C_{11}-pyrogallol[4]arene (**2**) capsules. In this study, we investigated the encapsulation of two bulky and structurally related isosteric guests namely adamantane-1-carboxylic acid (**3**) and 3,5,7-trifluoro adamantane-1-carboxylic acid (**4**) into these hexamers in a competitive (chloroform) and a non-competitive (benzene) solvent. Through the application of NMR spectroscopy, diffusion NMR, and ^{19}F guest exchange saturation transfer (GEST) applied for the first time on such hexameric capsules, we show that the two apparently similar hexamers behave differently towards these two isosteric guests. We found that in C_6D_6 the hexamers of **1** preferentially encapsulate the non-fluorinated guest **3** over guest **4**, while the hexamers of **2** preferentially encapsulate the fluorinated isosteric guest **4**. For the hexameric capsule of **2** encapsulating guest **4**, ^{19}F-NMR shows that the disruption of the hexameric capsule by methanol is a more complex process than one would have anticipated revealing, for the first time, three populations of **4** having different exchange rates. The combination of ^{1}H/^{19}F diffusion and ^{19}F-GEST NMR provides new insights into these important and catalytically active capsular systems demonstrating the advantages of using this combination of NMR methods to explore such supramolecular systems in solution.

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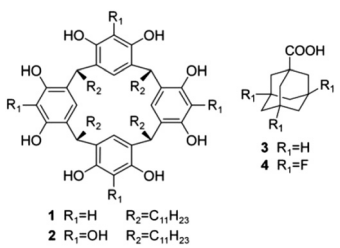
Introduction

During the last decades self-assembled molecular capsules and cages of different natures were prepared.[1–9] Among those, the hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes are perhaps the most intriguing, highly accessible and fascinating molecular capsules known.[10–18] These self-assembled hexameric capsules having large cavities were observed first in the solid state and then in solution and in the gas phase.[10–18] Shyvaniuk and Rebek showed that by using a suitable guest it is possible to probe, unequivocally, the existence of such hexameric capsules of lipophilic resorcin[4]arene in chloroform.[13] Diffusion NMR showed that, surprisingly, hexameric capsules are indeed the resting state of lipophilic resorcin[4]arenes and pyrogallol[4]arenes like **1** and **2** (Scheme 1) in common organic solvents.[14–17] These diffusion NMR studies were instrumental in the characterization of the solution structures of these hexamers showing that in chloroform **1** forms $(\mathbf{1})_6(H_2O)_8$-type capsules, whereas **2** forms $\mathbf{2}_6$-type capsules.[14–16] Diffusion NMR also enabled us to show that these hexamers self-sort, and that their self-assembly process results exclusively in homo-hexamers when resorcin[4]arenes and pyrogallol[4]arenes are mixed.[17] These results were then reproduced by fluorescence spectroscopy.[19] Very recently, we



Scheme 1 The structures of compounds **1**, **2**, **3** and **4**.

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could demonstrate that **2** forms only hexameric capsules both in chloroform and in non-competitive solvents such as benzene and toluene. Compound **1**, however, was found to form hexameric capsules and higher aggregates as a minor product in non-competitive solvents like benzene and toluene.[20] This is in contrast to what was recently claimed using small angle neutron and X-ray diffraction (SANS and SAXS, respectively).[21,22] Note, however, that the minor product of **1** observed in benzene and toluene appears to have an octameric structure according to diffusion NMR measurements.[20] In addition, the hosting capability of the two types of hexamers was found to differ.[23–31] Catalysis was performed mostly in the resorcin[4]arene capsules, first by Scarso,[32,33] and then by the Tiefenbacher and Neri groups.[34–40] In some of the cases, the acidic water molecules of the hexameric capsule of **1** were said to play a pivotal role in the catalysis.[41] Moreover, it was demonstrated that water molecules that are part of the hexameric capsule of **1**, are essential for various reactions performed within the hexameric capsules of the lipophilic resorcin[4]arene.[42] At least in one case, the lack of water molecules in the structure was blamed for the catalytic incompetence of the hexameric capsules of pyrogallol[4]arene.[41] Note that different computational studies were performed on the peculiar hexamer of **1** [43–45] and a very recent experimental and computational study suggested that the hexameric capsule of **1** with 14 water molecules is the most active species in the catalysis.[46] Additionally, following our demonstration that ammonium salts can be encapsulated in the pyrogallol[4]arene hexamers in a non-competitive solvent like benzene,[47] it was recently shown that these hexameric capsules affect the product distribution and may have some catalytic effects on 1,3 dipolar addition reaction in that solvent.[48] All the above facts highlight the differences between the seemingly similar hexamers of **1** and **2**. Some of the above observations and findings about these capsules are, in fact, difficult to reconcile.

Results and discussion

In this study, we decided to use a pair of bulky isosteric guests and to investigate their interactions with the capsules of **1** and **2** (Scheme 1) in both competitive and non-competitive solvents. Here we report on the encapsulation of adamantane-1-carboxylic acid (**3**) and 3,5,7-trifluoro adamantane-1-carboxylic acid ((**4**), Scheme 1) into the hexameric capsules of **1** and **2** both in chloroform and in benzene.

Fig. 1 shows the ^{1}H-NMR spectra of solutions of 30 mM of **1** and 10 mM of **3** and **4** in $CDCl_3$ and C_6D_6. Fig. 2 shows the same data for solutions of **2** and the two isosteric guests, namely **3** and **4**. From the high-field ^{1}H-NMR signals of guest **3** in the solutions with **1** presented in Fig. 1a and b, we could conclude that guest **3** is encapsulated in the hexameric capsules of **1** both in $CDCl_3$ and in C_6D_6. The isosteric guest **4** shows lower affinity toward the cavity of the hexamers of **1** in C_6D_6 (Fig. 1c). In $CDCl_3$, we see no clear evidence for encapsulation of **4** into the hexameric capsule of **1** (Fig. 1d). Fig. 2

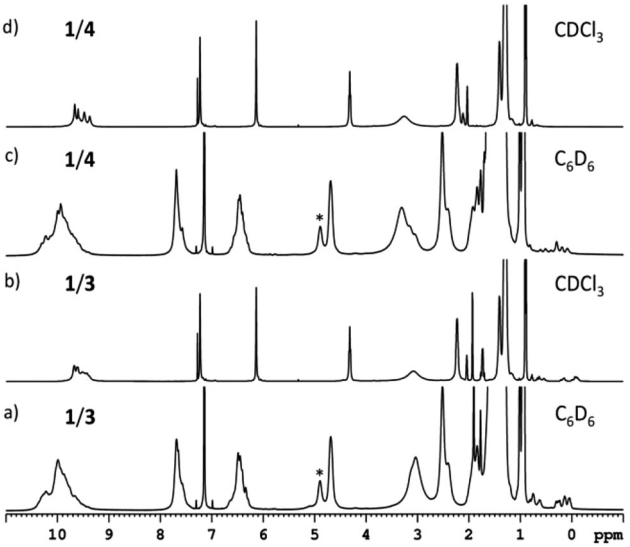

Fig. 1 ^{1}H-NMR spectra (500 MHz, 298 K) of the solutions of 30 mM of **1** and 10 mM of **3** (a and b) and **4** (c and d) in C_6D_6 (a and c) and $CDCl_3$ (b and d). The * symbols represent the signals of the higher aggregates of **1** in C_6D_6.

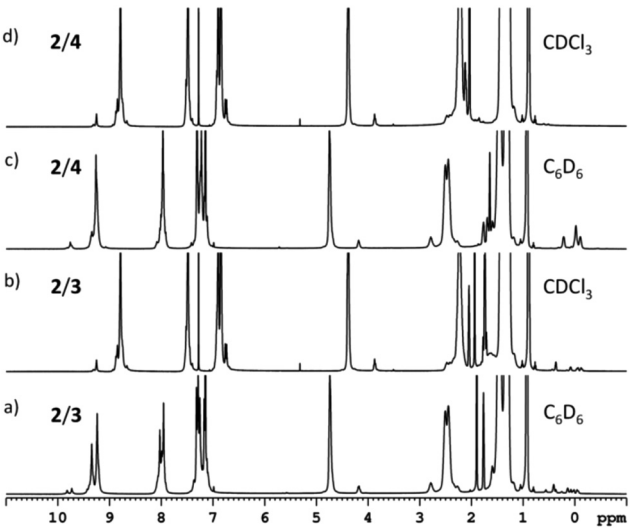

Fig. 2 ^{1}H-NMR spectra (500 MHz, 298 K) of the solutions of 30 mM of **2** and 10 mM of **3** (a and b) and **4** (c and d) in C_6D_6 (a and c) and $CDCl_3$ (b and d).

shows somewhat different behaviour for the hexameric capsules of **2**. There we observe some encapsulation of **3** into the hexameric capsules of **2** in C_6D_6 and in $CDCl_3$ (Fig. 2a and b). The isosteric guest **4** is, however, significantly encapsulated in the hexameric capsule of **2** in C_6D_6, but not at all in the $CDCl_3$ solution (Fig. 2c and d). The encapsulation of **4** (Fig. 2c) in C_6D_6 is favoured compared to **3** (Fig. 2a), which is opposite to the trend observed for the capsule of **1** (Fig. 1c and a). This was also validated by integration of the relevant ^{1}H-NMR

signals in the C_6D_6 solutions (Table S1 in the ESI†). Table S1† shows that, in C_6D_6, the integration ratios, of the hexameric capsule of **1** and encapsulated guests **3** and **4** are 1 : 0.45 and 1 : 0.28, respectively, showing a higher affinity of the capsules of **1** to **3** compared to **4**. However, for the capsule of **2**, the integration ratios of the capsule of **2** and the encapsulated guests **3** and **4** are 1 : 0.18 is 1 : 0.40, respectively, indicating a clear preference of the hexameric capsule of **2** to guest **4** over guest **3**.

Next, we employed diffusion NMR, a technique that has been extensively used to study such systems,[14–17,20,49–52] to show that the encapsulation is taking place in the hexameric capsules of **1** and **2**. This was concluded based on the results of the diffusion NMR measurements of **1** and **2** in the presence of **3** and **4** across the various $CDCl_3$ solutions, both before and after the addition of methanol. The results are presented in Fig. 3 and Table S2.† Indeed, the extracted diffusion coefficients are consistent with the formation of hexameric capsules encapsulating guests **3** and **4** that are disrupted to their respective monomers by the addition of methanol. This disruption is manifested by the dramatic increase in the diffusion coefficients of **1** and **2** upon addition of methanol, coupled with the disappearance of the high-field ^{1}H-NMR signals assigned to the encapsulated guests. Very similar results were also observed when methanol was added to the C_6D_6 solutions of **1** and **2** with **3** and **4**.

Next, we decided to collect the ^{19}F-NMR spectra of the solutions of **1** and **2** with the fluorinated guest **4**, which are presented in Fig. 4. These ^{19}F-NMR spectra reveal that for the hexameric capsule of **1** the signals of encapsulated guest **4** are located at lower field compared to the peak of the free guest (Fig. 4a and b, marked with arrows). Conversely, for the hexameric capsule of **2**, we observe, in C_6D_6, a relatively strong signal which, surprisingly, is at a high-field (Fig. 4c, marked with an arrow) compared to the signal of the free guest. In contrast, for the $CDCl_3$ solution of **2** and **4** we observe no signal of the encapsulated guest (Fig. 4d) which is consistent with the ^{1}H-NMR spectrum presented in Fig. 2d. The next step was to verify that the signal at high-field in the ^{19}F-NMR spectrum of the C_6D_6 solution of **2** and **4** is indeed that of **4** encapsulated in the hexamer of **2**. For this purpose, we measured the diffusion coefficient of that signal in the ^{19}F-NMR spectrum (Table S3†) and compared it to the diffusion coefficient of signals of **2** in that solution extracted from ^{1}H diffusion NMR which was 0.20 ± 0.01 × 10^{-5} cm^2 s^{-1}. As expected, we found the two diffusion coefficients to be similar within the experimental error, corroborating even further that this high-field ^{19}F-NMR signal represents encapsulated **4** in the hexamer of **2**.

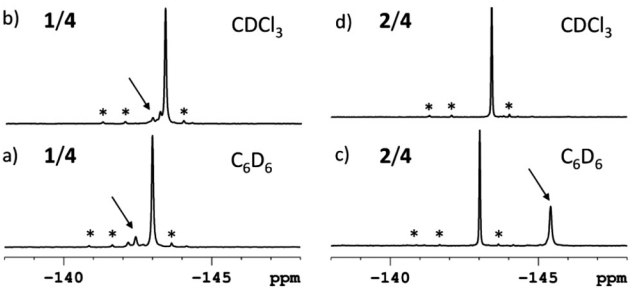

Fig. 4 ^{19}F-NMR spectra (470 MHz, 298 K) of the 30 mM solutions of **1** (a and b) and **2** (c and d) in the presence of 10 mM of **4** in C_6D_6 (a and c) and $CDCl_3$ (b and d). The * symbols represent minor impurities. Arrows indicate the peaks of encapsulated guest.

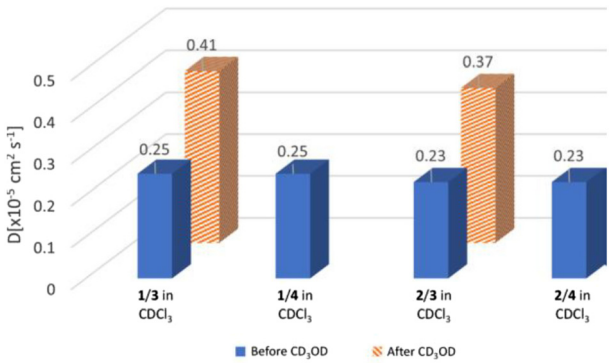

Fig. 3 Diffusion coefficients of **1** and **2** for the solutions presented in Fig. 1(b, d) and 2(b, d) both before and after addition of CD_3OD. To the 0.5 ml solutions of **1/3** and **2/3**, 45 μl and 150 μl of CD_3OD were added, respectively. The diffusion coefficients are averages ± SD of three independent measurements. SD values were equal or smaller than 0.01 × 10^{-5} cm^2 s^{-1} in all cases.

Since the fluorinated guest **4** that is encapsulated in the hexameric capsule of **2** gave a distinct and significantly shifted ^{19}F-NMR signal we thought to use chemical exchange saturation transfer (CEST) NMR experiment[53] to glean, for the first time, quantitative information about the in–out exchange rate of a guest in such hexameric capsules. For the quantitative analysis, we chose to use the ^{19}F-NMR multi power guest exchange saturation transfer (GEST) experiment, recently suggested by the Bar-Shir group.[54–58] To obtain an accurate estimation of the guest exchange rate using the aforementioned methodology, we had to increase even further the ratio between unbound and bound guest. We achieved that by increasing the concentration of **4** in the solutions from 10 mM to 100 mM.

Fig. S1 and S2 in the ESI† show the same data as in Fig. 1 and 2 but for solutions where the guest concentrations are 100 mM. The ^{1}H-NMR spectra presented in these Figures show essentially the same information as that presented in Fig. 1 and 2. Before performing the ^{19}F-GEST NMR experiments, we performed a detailed titration of the solution presented in Fig. S2c† using CD_3OD. This titration was followed by ^{1}H- and ^{19}F-NMR and the results are presented in Fig. S3† and Fig. 5, respectively. The ^{1}H-NMR spectra presented in Fig. S3† show small changes upon addition of the first 2 μl of CD_3OD. After addition of 6–8 μl of CD_3OD significant line broadening and some line shape changes are observed. Following the addition of 10–12 μl of CD_3OD, there is almost a complete dis-

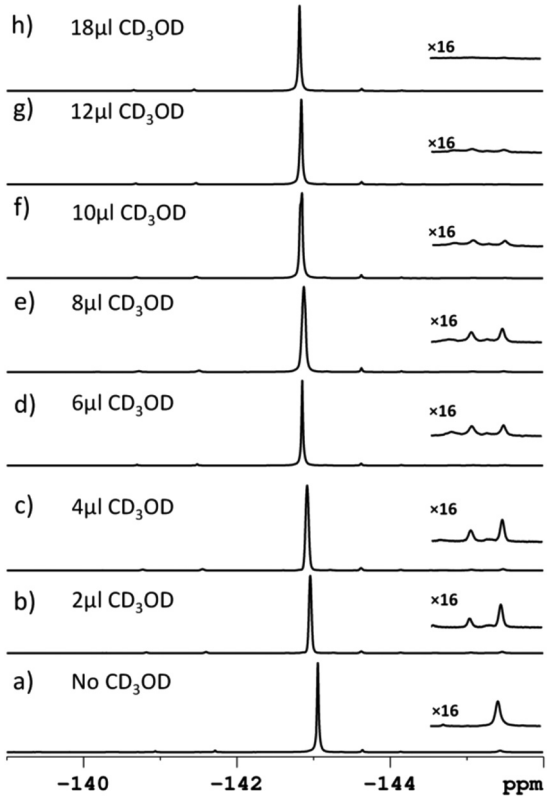

Fig. 5 ^{19}F-NMR spectra (470 MHz, 298 K) of the 30 mM solutions of **2** in the presence of 100 mM of **4** in C_6D_6 (a) before and after addition of (b) 2 μl, (c) 4 μl, (d) 6 μl, (e) 8 μl, (f) 10 μl, (g) 12 μl, and (h) 18 μl of CD_3OD.

appearance of the ^{1}H-NMR signals of the encapsulated guest, as shown in Fig. S3f and g.† Addition of 18 μl of CD_3OD results in practically complete disappearance of the signals of the encapsulated guest from the ^{1}H-NMR spectrum (Fig. S3h†). However, the ^{19}F-NMR spectra presented in Fig. 5 appear to reveal more details about the process. Fig. 5b and c show that addition of 2–4 μl of CD_3OD to the solution results in the splitting of the original signal in the ^{19}F-NMR spectrum of the encapsulated guest **4**, accompanied by the appearance of a new signal just 0.2 ppm away from this signal. Adding an extra 2 μl of CD_3OD to this solution results in a further decrease in the intensity of the original ^{19}F-NMR signal at −145.7 ppm and a further increase of the new signal (Fig. 5d). After addition of 8 μl of CD_3OD one observes in fact three weak signals, two of similar intensity and a third one which is much weaker in intensity (Fig. 5e). Addition of more CD_3OD results in further broadening and reduction in the intensity of the ^{19}F-NMR signals of encapsulated **4**. After addition of 18μl of CD_3OD these signals appear to vanish from the one pulse ^{19}F-NMR spectrum. These results suggest that indeed addition of CD_3OD weakens the hydrogen bonds holding the hexamers and that this process is accompanied by the formation of three pools of encapsulated **4**.

The ^{19}F-GEST NMR experiments were performed on a C_6D_6 solution presented in Fig. 5 both before and after addition of 8, 12 and 18 μl of CD_3OD and the results are presented in Fig. 6. For the samples presented in Fig. 6 we concomitantly measured the diffusion coefficients of all molecular species observed in the ^{1}H- and ^{19}F-NMR spectra of those samples. This was performed to monitor the effect of methanol addition on the aggregation mode of the system and the results are presented in Tables S4 and S5.† The results of the multi-B1 ^{19}F-GEST NMR experiments performed on the C_6D_6 solution of **2** and **4** show that without the addition of methanol, the in–out exchange is too slow to be measured using the aforementioned methodology (Fig. 6a). Addition of up to 4 μl of CD_3OD had a marginal effect on the line shape of the signals at high-field in the ^{1}H-NMR spectrum, which are attributed to encapsulated guest, and had no effect on the diffusion coefficients of all signals, including those of the encapsulated guest. However, some changes were already observed in the ^{19}F-NMR spectra for the signals attributed to the encapsulated guest **4** (Fig. 5a and b). Under these experimental conditions, the GEST experiment showed no effect, probably because the release of the guest is still slow in the NMR timescale. The addition of 8 μl of CD_3OD to the C_6D_6 solution of **2** and guest **4** resulted in significant changes of the signals of the encapsulated guest in the ^{1}H-NMR spectrum (Fig. S3e†), and significant reduction in the intensity and splitting of the ^{19}F-NMR signal of encapsulated **4** into three signals (Fig. 5e). Note that the addition 8 μl of CD_3OD had no effect on the diffusion coefficient of **2**, implying that the hexamers are still intact (Table S4†). For this solution however, a clear GEST effect was observed (Fig. 6b) from which a quantitative analysis revealed three signals exchanging in not equal but similar k_{out} values in the range of less than 30 s^{-1}.

After addition of 12 μl of CD_3OD to this C_6D_6 solution, we observe further broadening of the ^{1}H/^{19}F-NMR signals of the encapsulated guest (Fig. S3g,† and Fig. 5g) but the diffusion coefficient of the system remained unchanged (*i.e.*, 0.18 ± 0.01 × 10^{-5} cm^2 s^{-1}), implying that the hexameric capsules of **2** are still intact. Here, a stronger ^{19}F-GEST response was observed (Fig. 6c) and slightly higher k_{out} values of about 81 ± 4, 29 ± 2 and 50 ± 15 s^{-1} were extracted. After addition of 18 μl of CD_3OD to the C_6D_6 solution, we observe a disappearance of the ^{1}H/^{19}F-NMR signals of the encapsulated guest (Fig. S3h† and Fig. 5h) and some increase in the diffusion coefficient of the system (Table S4†). This increase, however, appears to represent mostly some decrease in viscosity as manifested by the increase in the diffusion coefficient of the solvent itself. There, the extracted k_{out} values were higher and were found to be 731 ± 66, 152 ± 11 and 72 ± 11 s^{-1} (Fig. 6d).

Clearly, as expected, the release rate of the encapsulated guest increased with the increase in the amount of methanol added to the benzene solution of **2** and **4**. Interestingly, even after complete disappearance of the ^{1}H- and ^{19}F-NMR signals of the encapsulated guest in the one-pulse experiments, we still monitor relatively slow k_{out} exchange rates of guest **4** from the capsule of **2**. It is important to note that after addition of 18 μl of CD_3OD to the C_6D_6 solution, we observed three distinct k_{out} values. The exchange rate for the original ^{19}F NMR

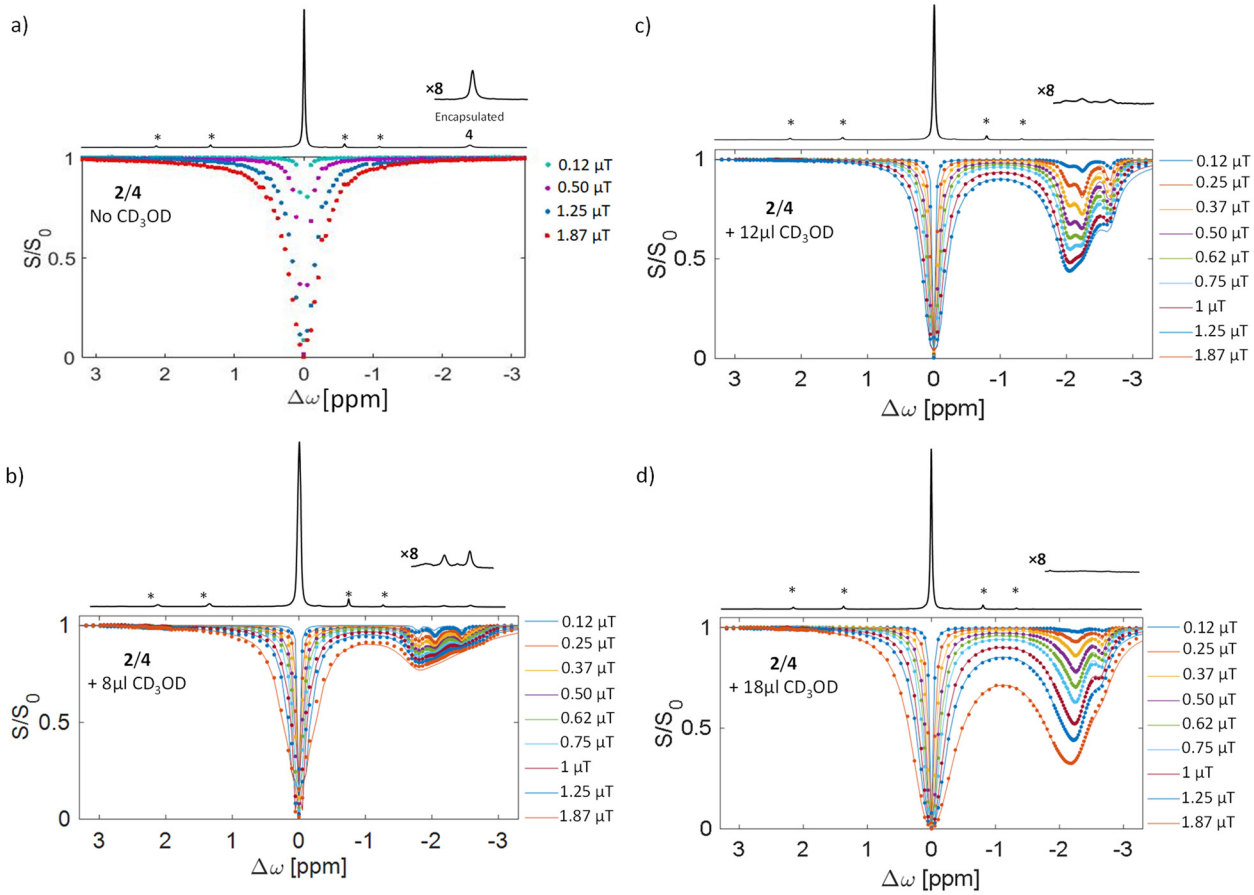

Fig. 6 ^{19}F-NMR spectrum (upper part) and the multi-B1 ^{19}F-NMR GEST spectra (lower part) of the C_6D_6 solution of 30 mM of **2** and 100 mM of **4** (470 MHz, 298 K) (a) before and after addition of (b) 8 μl, (c) 12 μl, and (d) 18 μl of CD_3OD. The points represent the experimental data and solid lines are the results of the fittings based on the Bloch–McConnell equations[59] as described recently.[58,60–62] The * symbols represent signals of minor impurities.

signal of encapsulated guest **4** is the one that show the slowest exchange rate. The new ^{19}F-NMR signals observed near the original signal of the encapsulated fluorinated guest **4** may be attributed to **4** encapsulated in slightly modified hexameric capsules or to a second molecule of **4** within the same capsule. Note that the volume of **4** is less than 200 Å^3 which, according to the 55% packing rule of Rebek,[63] implies that, in principle, two molecules of **4** can be encapsulated in each hexamer of **2**. Moreover, in the ^{19}F 2D-NOESY NMR experiment performed on the sample presented in Fig. 2c after addition of 8 μl of CD_3OD, we indeed found cross-peaks between the two strongest signals attributed to encapsulated **4** as shown in Fig. S4.† These cross-peaks imply that these two species are in close vicinity to each other, corroborating the assumption that these two signals arise from two encapsulated species in the same capsule. Despite all these findings, it is still relatively difficult to pinpoint, unequivocally, on the exact structural nature of the specific hexameric capsules involved in the exchange after methanol addition to the solution **2** and **4** in benzene. What is clear is that the high sensitivity of the fluorine chemical shift and the ^{19}F GEST NMR experiments enabled to demonstrate, for the first time, that the methanol disintegration of these hexameric capsules is a more complex process than one would have anticipated involving some transient capsules.

Experimental

Materials

All starting materials, reagents, guests' molecules, and deuterated solvents were purchased from Sigma-Aldrich and used as received. Compounds **1** and **2** were synthesized according to ref. 14 and 17.

NMR

^{1}H- and ^{19}F-NMR experiments were collected on 11.7T Avance III Bruker instrument operating at 500.1 and 470 MHz, respectively.

Diffusion NMR

^{1}H- and ^{19}F-NMR diffusion experiments were collected with longitudinal eddy current delay (LED) sequence.[64] For more details, see ESI.†

^{19}F GEST

^{19}F-NMR GEST experiments were collected and analysed according to ref. 57–62 For more details, see ESI.†

Conclusions

In conclusion, we studied the encapsulation of two bulky isosteric guests namely **3** and **4** into the hexameric capsules of **1** and **2**, in competitive and non-competitive solvents such as chloroform and benzene, respectively. We found that encapsulation of **4** is more efficient in benzene than in chloroform. Interestingly, we found that while the hexamers of **1** preferentially encapsulate the non-fluorinated guest **3** over guest **4**, the hexamers of **2** preferentially encapsulate the fluorinated isosteric guest **4**. Surprisingly, only in the case of **2** and only in benzene the fluorinated encapsulated guest **4** had a strong, distinct and high-field shifted signal in the ^{19}F-NMR spectrum. This signal enabled us to measure, for the first time in such systems, the in–out exchange rate using the ^{19}F-GEST approach. This measurement together with diffusion NMR show that, after addition of minute amounts of methanol, exchange of this bulky guest out from the hexamers is possible while the hexamers of **2** still prevail in the solution. The ^{19}F-GEST NMR experiments reveal that the disruption by methanol of the hexamers of **2** encapsulating **4** is a more complex process than one may have anticipated, revealing three populations of **4** having different exchange rates. Before the addition of methanol to the hexamers of **2** in benzene no in–out exchange could be measured for **4** using the ^{19}F-GEST NMR experiment. All these findings demonstrate on the different characteristics and guest affinity of the two apparently similar resorcin[4]arene and pyrogallol[4]arene hexamers. The present study shows that the combination of advanced NMR methods such as ^{1}H/^{19}F diffusion NMR and ^{19}F-GEST NMR experiments provides new insights on these important and well-studied, catalytically active capsular self-assembled systems.

Author contributions

Y. C. and L. A. conceived the project. T. S. and I. H. performed the synthesis and characterization of the compounds. S. S. performed the ^{19}F GEST experiments with the supervision of L. A. Y. C. wrote the paper with S. S. and L. A. All authors participated in reviewing the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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