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Unique Organization of Solvent Molecules Within the Hexameric Capsules of Pyrogallol[4]arene in Solution

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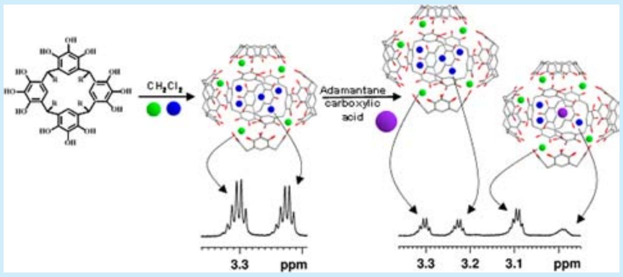
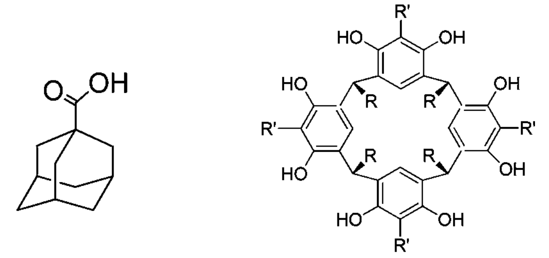
Supporting Information

ABSTRACT: The hexameric capsules of pyrogallol[4]arene (**2b**) were prepared in nondeuterated solvents in the absence and presence of adamantane carboxylic acid (**3**). The small encapsulated molecules were shown to occupy different sites within the same capsule. In the presence of **3**, which are also encapsulated in the hexameric capsules, one observes yet another pair of signals for the encapsulated solvent molecules. Different NMR experiments enabled assignment of the different sites within the hexameric capsules of **2b**.



Scheme 1. Chemical Structures



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1a R' = H R = CH_3
1b R' = H R = $C_{11}H_{23}$
2a R' = OH R = isobutyl
2b R' = OH R = $C_{11}H_{23}$

Resorcin[4]arenes and pyrogallol[4]arenes were synthesized more than a century ago;[1] however, it was only the seminal paper of the Atwood group, published in 1997, that showed that **1a** (Scheme 1) forms hexameric capsules in the solid state.[2] Subsequently Mattay et al. reported that **2a** also forms hexamers in the solid state,[3] and the Rebek group found, in 2001, that hexamers of **1b** can be observed in solution in the presence of suitable guests.[4] Soon after, Avram and Cohen demonstrated, with the aid of diffusion NMR, that hexameric capsules are the resting states of lipophilic resorcin[4]arenes and pyrogallol[4]arenes in nonpolar organic solvents even in the absence of any specific guests, demonstrating, in fact, that the solvent molecules serve as encapsulated guests in these hexamers.[5] All these studies have dramatically changed the way we conceive the structures of such systems in nonpolar organic solvents.[6] Despite the resemblance of the structure of **1** and **2**, soon it became apparent that, in solution, the hexamers of resorcin[4]arenes and pyrogallol[4]arenes differ.[5] It was found that **1** forms $1_6(H_2O)_8$-type hexamers while **2** forms 2_6-type hexamers in solutions, thus providing insights into why the self-assembly of resorcin[4]arenes and pyrogallol[4]arenes proceeds with self-sorting affording only homohexamers when mixed together.[5d,7] In addition, it was found that the pyrogallol[4]arene hexamers are able to encapsulate only a few guests compared to resorcin[4]arene hexamers which were shown to encapsulate alcohols, amines, ammonium salts, acids, esters, and more.[8] This dramatic difference urged, recently, the Purse group to use the melting approach to increase the repertoire of guests that can be encapsulated in **2b**.[9] In addition, the ^1H NMR spectrum of the encapsulated $CHCl_3$ molecules in the hexamers of **2b** was found to be significantly more structured than that of the $CHCl_3$ molecules encapsulated in the hexamers of **1b**.[10] Although the signal of the encapsulated $CHCl_3$ molecules in the capsules of **2b** appears as a multiplet, it is in fact a series of different singlets (Figure 1A).[10]

It was concluded, based on different NMR experiments, that the peculiar signal of the encapsulated $CHCl_3$ molecules consists of seven singlets having relative intensity distribution reminiscent of what is expected from six one-half spins.

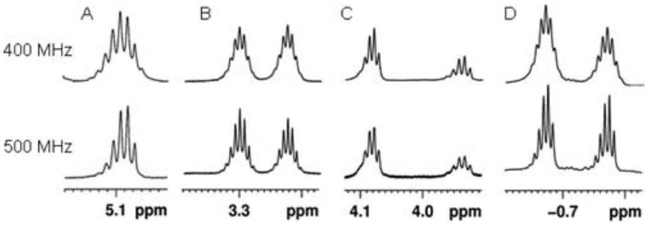

Figure 1. Extracts of the ^1H NMR spectra (400 and 500 MHz, 298 K) showing only the peaks of the encapsulated solvent molecules in the hexamers of **2b** in (A) $CHCl_3$, (B) CH_2Cl_2, (C) $CHBr_3$, and (D) CH_3I.

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Therefore, it was suggested that this peculiar signal originates from the seven stereochemical possibilities to organize the **2b** monomers in **2b**$_6$.[10]

As the information regarding guests organization in such large spherical capsules in solution is scarce, we decided to study the self-assembly of **2b** in a series of nondeuterated nonpolar organic solvents both in the absence and in the presence of adamantane carboxylic acid (**3**). We used a combination of NMR methods with the aim of explaining the peculiar spectra of the encapsulated solvent molecules within the inner cavity of the hexameric capsules of **2b**.

Figure 1 shows the ^{1}H NMR spectra of different solvents encapsulated in the hexamers of **2b**. Figure 1B shows that the spectrum of the encapsulated CH_2Cl_2 consists of two signals in an ~1:1 ratio each composed of seven singlets. One may assume, at first glance, that the origin of the pair of signals observed in the case of CH_2Cl_2 is the two protons of the molecules; however, interestingly, we observe the same phenomenon also for the other encapsulated solvents, i.e. $CHBr_3$ and CH_3I, regardless of the number of protons in the encapsulated molecules (see Figure 1C and 1D, respectively). In addition, Figure 1C and 1D show that the intensity ratio between the two signals in those solvents differs from the 1:1 ratio observed in the case of CH_2Cl_2. The ^{1}H NMR spectra of the encapsulated solvent molecules were recorded in two different magnetic fields (Figure 1). It was found that the separation between the peaks (in Hertz unit) for all solvents increases with the increase in the magnetic field. This implies that the two signals are not coupled multiplets but each constitute seven singlets as in the case of encapsulated $CHCl_3$ (Figure 1A).[10]

To shed light on the origin of these observations the 2D COSY, 2D NOESY, and 2D ROESY spectra of these hexamers in the different nondeuterated organic solvents were collected. Figures 2A, 2C, and 2E show the COSY, NOESY, and ROESY peaks of the OH's and the aromatic proton of the hexamer while Figure 2B, 2D, and 2F show the respective information for peaks representing the encapsulated CH_2Cl_2 molecules. Clearly, the absence of cross-peaks in the COSY spectrum between the two signals of the encapsulated solvent molecules (Figure 2B) and the appearance of cross-peaks in the NOESY and ROESY (Figure 2D and 2F) demonstrate that there are two types of encapsulated CH_2Cl_2 molecules in a single hexameric capsule of **2b**. To explain the origin of the mechanism responsible for the cross-peaks of the encapsulated solvent molecules we compared the relative phases of the NOESY and ROESY cross-peaks of the encapsulated CH_2Cl_2 molecules with those of **2b** where only NOE effects may be operative. Indeed, we found that the NOESY cross-peaks shown in Figure 2C and 2D have the same phases while the ROESY cross-peaks shown in Figure 2E and 2F have opposite phases. These observations suggest that the encapsulated CH_2Cl_2 molecules exchange magnetization through the exchange mechanism rather than through direct NOE. Figure S1 in the Supporting Information (SI) shows that this is indeed the case also for the encapsulated CH_3I molecules.

When the hexameric capsule of **2b** was prepared in the nondeuterated solvents in the presence of 5 equiv of **3**, the spectra shown in Figures 3Ab, 3Bb, and 3Cb were obtained. These spectra show that indeed **3** is also encapsulated in **2b**$_6$. The spectra presented in Figure 3 also demonstrate that when **3** is present in the solution and is encapsulated in the hexamers of **2b**, two pairs of signals, i.e. four signals each appearing as a multiple of singlets (Figure 3Ab, 3Bb, 3Cb), are observed for the encapsulated solvent molecules. Comparison of the spectra presented in Figure 3 shows that when **3** is encapsulated, two of the four peaks of the encapsulated solvent molecules are those of the encapsulated solvent molecules in the absence of **3**. Figure 3D shows that the diffusion coefficients of the encapsulated solvent molecules and the encapsulated **3** molecules are the same as that of **2b** in all three solvents, meaning that each of these systems diffuse as a single molecular

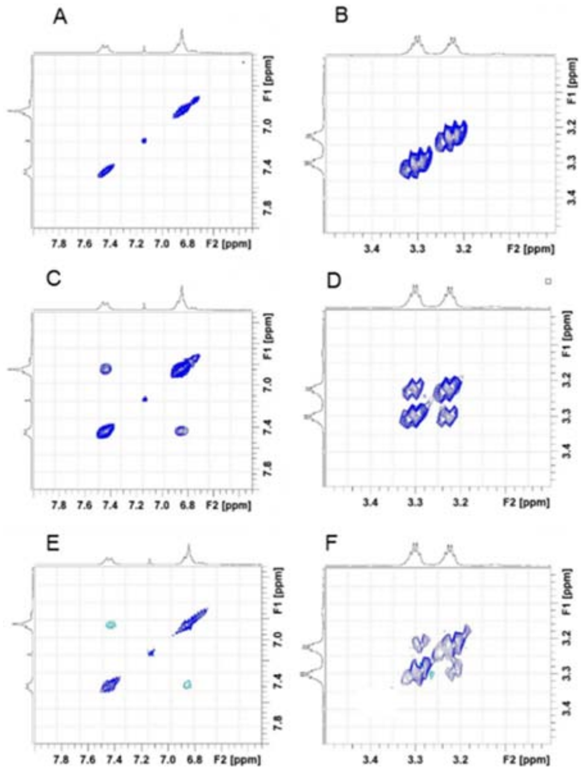


Figure 2. Extracts of the 2D ^{1}H NMR spectra (500 MHz, 298 K) showing two peaks of **2b** (A,C,E) and peaks of the encapsulated CH_2Cl_2 molecules (B,D,F) in the hexamers of **2b**. (A,B) COSY, (C,D) NOESY, and (E,F) ROESY. The cyan cross-peaks are in an opposite phase of the blue cross-peaks.

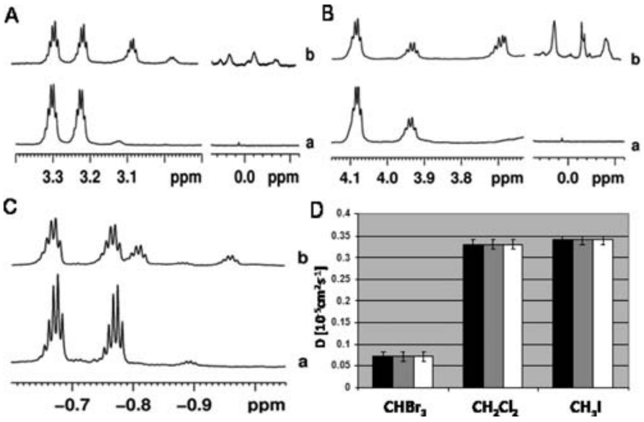
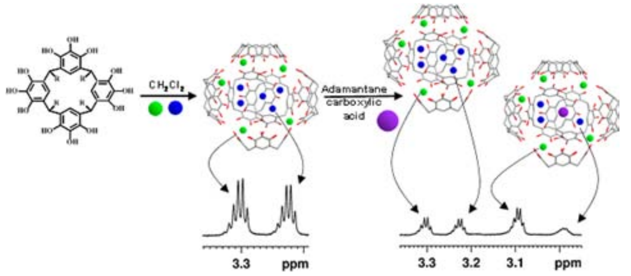


Figure 3. Extracts of the ^{1}H NMR spectra (500 MHz, 298 K) showing only the peaks of the encapsulated solvent molecules and encapsulated **3** in the hexamers of **2b** in the absence (a) and presence (b) of 5 equiv of **3** in (A) CH_2Cl_2, (B) $CHBr_3$, and (C) CH_3I. (D) The diffusion coefficients of **2b** (black), encapsulated solvent molecules (gray), and encapsulated **3** (white) in different solvents.

entity.[11] These results imply that two types of hexamers prevail in the solution as shown in Scheme 2.

Scheme 2. Sites Occupied by Encapsulated Solvent Molecules in the Hexamers of 2b



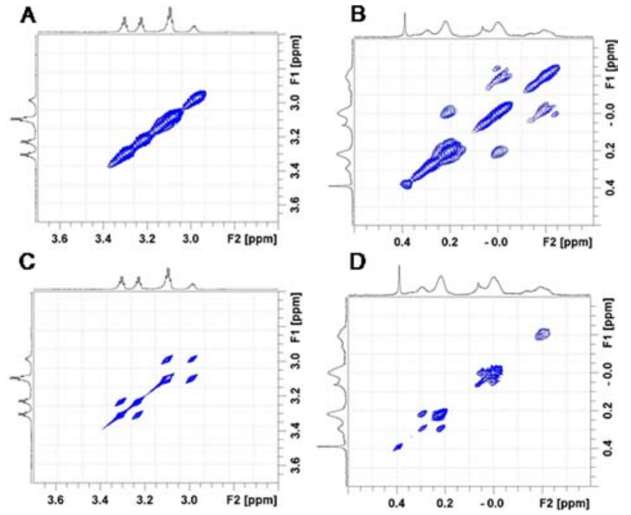


Figure 4. Extracts of the 2D (A,B) COSY and (C,D) NOESY ^{1}H NMR spectra (500 MHz, 298 K) showing only the peaks of the encapsulated CH_2Cl_2 molecules (A,C) and encapsulated **3** (B,D) in the hexamers of **2b** in the presence of 5 equiv of **3** in CH_2Cl_2.

The sections of the 2D COSY and NOESY spectra presented in Figure 4, collected from the CH_2Cl_2 solution of **2b**$_6$ in the presence of excess **3**, also corroborate these conclusions. From Figure 4 it can be concluded that there are two types of hexameric capsules in the solution, one which encapsulates only solvent molecules that occupy two distinct sites and another type of hexamers that encapsulates a molecule of **3** and additional solvent molecules which apparently also occupy two distinct positions in the hexamers. Interestingly, in the hexamers that encapsulate **3** the occupancy ratio between the two sites is different clearly showing a higher population in one of the sites. It seems that **3** preferably occupies the inner site for which peaks appear at higher field. To substantiate this assignment we performed a series of 1D-ROE experiments on the system shown in Figure 4.

Figure 5 presents the normalized intensity (I/I_s) of the peaks in 1D-ROE NMR experiments when irradiating the peaks of the encapsulated CH_2Cl_2 molecules (I_s) at 3.3 or 3.2 ppm. Figure 5 shows that the peaks of the encapsulated solvent molecules at 3.3 ppm exchange magnetization more with the solvent molecules in the bulk as compared to the peak at 3.2 ppm. This is true also for hexamers of **2b** in the presence of **3** (see Figure S2 in the SI). More importantly, the 1D-ROEs presented in Figure 5 also show that only the peaks of the encapsulated CH_2Cl_2 molecules at 3.3 ppm transfer magnetization to peaks of the hexamers of **2b** while the peaks at 3.2 ppm do not. The same is observed for the pair of peaks of the encapsulated CH_2Cl_2 when **3** is also encapsulated in the hexamer of **2b** (see Figure S2 in the SI). Therefore, one can conclude that the signals at higher field of each pair represent the encapsulated CH_2Cl_2 molecules in the center of the hexamers while the other peaks represent solvent molecules which are closer to the macrocycle and reside in the outer belt layer of the encapsulated solvent molecules (see Scheme 2). These solvent molecules are therefore exchanging magnetization with **2b**. This assignment is in line with the fact that the bulkier guest **3** preferably occupies the inner belt of the encapsulated solvent molecules at the center of the hexamers.

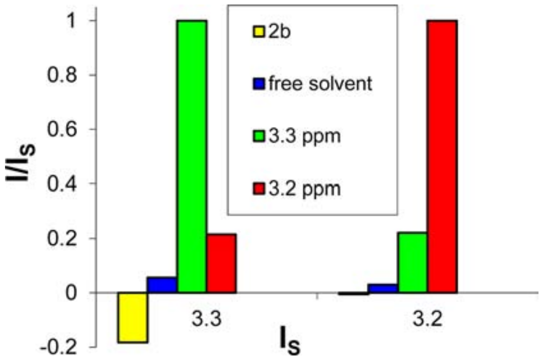


Figure 5. Normalized signal changes (I/I_S) upon irradiation of the peaks (I_S) of the encapsulated CH_2Cl_2 molecules at 3.3 (left) and 3.2 ppm (right).

Interestingly, when the hexamers were heated in the magnet in $CHBr_3$, a solvent which shows a pair of singlets and has a high boiling point, we observed that the signal in the low field disappears first upon increasing the temperature despite that at room temperature it is the dominant peak (see Figure 6A to 6G). By increasing the temperature the encapsulated solvents

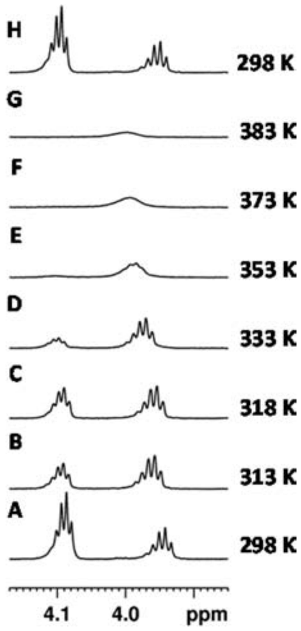


Figure 6. Extracts of the ^{1}H NMR spectra (500 MHz) showing only the peaks of the encapsulated $CHBr_3$ molecules in the hexamer of **2b** at different temperatures (A−G) and after cooling back to 298 K (H).

appear to be released from the cavity of **2b**. The encapsulated solvent molecules which appear to be closer to the macrocycle are released first, which is shown by the gradual disappearance of the peak at 4.1 ppm. As the temperature is further increased the encapsulated solvent molecules at the center of the capsule appear to be also released from the capsules and the intensity of their signals, at 3.9 ppm, are significantly decreased. These observations are reversible, and cooling the sample regenerated the spectrum shown in Figure 6A (see Figure 6H). All these observations corroborate further the assignment of the low-field peaks to the encapsulated solvent molecules residing in the outer belt in closer proximity to the macrocyclic walls of the hexamers of **2b**.

Based on integration of the peaks of the encapsulated solvent molecules, it can be concluded that an average of approximatly 10 CH_2Cl_2 molecules, 6 $CHCl_3$, 10 CH_3I, 6 $CHBr_3$, and 8 CH_2Br_2 are encapsulated in each hexamer of **2b**. In all solvents studied in the present work, besides $CHCl_3$, we observe two distinct sites for the encapsulated molecules. Clearly, the bulkier the encapsulated solvent molecule is, the fewer solvent molecules that can be found in each hexamer of **2b**. Taking into account the number and the van der Waals volumes of the different solvent molecules encapsulated in the hexamers of **2b**, and assuming a hexamer volume of about 1300 Å^3,[9b] it appears that in the case of $CHCl_3$, where we observe mainly one site for the encapsulated solvent molecules, the % occupancy is significantly lower than the % occupancies calculated for the other encapsulated solvents (Table S1 in the SI). Therefore, it may well be that the high % occupancy is the reason for finding different sites, on the NMR scale, in the hexamers of **2b**. The % occupancies found appear somewhat lower than that expected from the 55% rule[13] and are reminiscent of the values found recently[9b] (Table S1 in the SI).

In conclusion, for all encapsulated molecules studied in the present work besides $CHCl_3$, two distinct sites were found for the encapsulated solvent molecules in the hexamer of **2b**. When molecules of **3** were added to the solution two additional sites for CH_2Cl_2, CH_3I, and $CHBr_3$ were observed. All the NMR measurements performed on these hexamers imply that the peaks of the encapsulated molecules at a higher field represent solvent molecules at the center of the cavity of the capsules while others reside in the outer belt of the cavity more adjacent to macrocyclic walls of the hexamers. These observations show that the solvent molecules occupy distinct sites in these large capsules and demonstrate that compressing solvent molecules in a confined space may significantly affect their NMR characteristics.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

2D spectra of **2b**$_6$ in CH_3I, 1D ROE of **2b**$_6$ in CH_2Cl_2 with **3**, and table of % occupancy. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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