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Molecules at Close Range: Encapsulated Solvent Molecules in Pyrogallol[4]arene Hexameric Capsules

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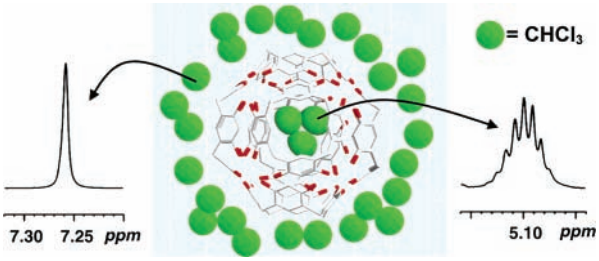
ABSTRACT



Pyrogallol[4]arenes form hexameric capsules with a large cavity and can be regarded as nanoreactors. The ^{1}H NMR signals of the encapsulated chloroform and benzene molecules are very complex, which may indicate that these encapsulated molecules are trapped in slightly different capsules. Co-encapsulation was found to be favored, and the ASIS effect was found to be enhanced, probably due to the close proximity and the higher molecular fraction of the benzene/chloroform complex in the capsule.

Molecular capsules are host systems that completely surround their guests, thus isolating them from the bulk and placing them in a distinct molecular environment.[1] In recent years, molecular capsules based on different noncovalent interactions were prepared.[2,3] Among these, hydrogen bond molecular capsules have attracted much interest, and dimeric and hexameric hydrogen bond molecular capsules were prepared.[1,2,4−6] In recent years, guest affinity, social and constellation isomerism, tautomeric equilibria, isotope effects, and diastereoism in such capsules were studied extensively, mostly by the group of Rebek.[1,7] However, the majority of these studies were performed on cylindrical dimeric capsules. Hexameric capsules of resorcinarenes and pyrogallolarenes (**1a** and **1b** in Figure 1) are complicated and hard to characterize in solution.[1a] These capsules have a large cavity that may accommodate a large guest or several small guests.

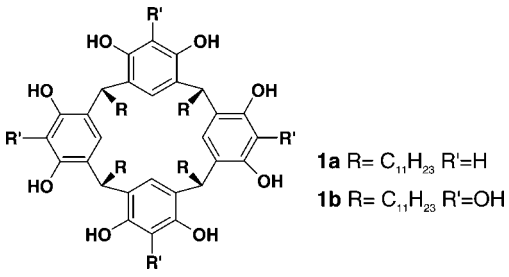


Figure 1. The structures of **1a** and **1b**.

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Despite the fact that the hexameric capsules of systems such as **1a** and **1b** became more popular recently,[8] detailed information regarding multiple hosts in such capsules is limited.[8i,l]

In the present paper, we studied the behavior of solvent molecules within the cavity of the molecular capsule of pyrogallolarene (**1b**) by different NMR techniques.

Pyrogallol[4]arene, **1b**, was prepared by the acid-catalyzed condensation of dodecanal with pyrogallol in 95% ethanol at room temperature over a period of 3 h.[9] The spectrum of **1b** in a $CHCl_3$ solution at 298 K is shown in Figure 2.

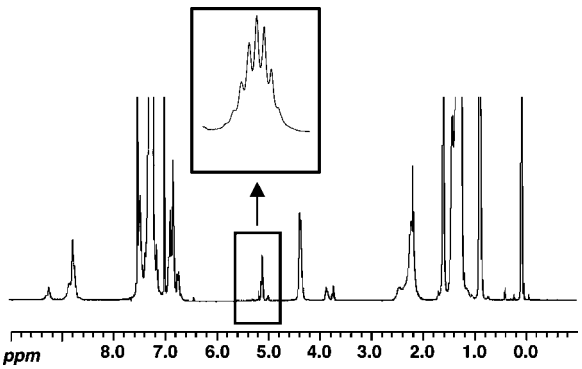

Figure 2. ^{1}H NMR spectrum (400 MHz, 298 K) of **1b** in a 20 mM $CHCl_3$ solution. The inset shows the enlargement of the peak attributed to the encapsulated chloroform molecules.

The spectrum of **1b** in $CHCl_3$ is the same spectrum as that of **1b** in $CDCl_3$, with an additional signal at 5.1 ppm. This signal is 2.2 ppm upfield from that of "free" $CHCl_3$ and was found to have the same diffusion coefficient[10] as that of **1b** within experimental errors ($0.24 \pm 0.01 \times 10^{-5}$ $cm^2\ s^{-1}$, 20 mM, 298 K). Therefore, it was attributed to the encapsulated chloroform molecules.

From the ^{1}H NMR integration, we concluded that 6−7 molecules of $CHCl_3$ are encapsulated in this hexameric capsule. A close look shows that this signal appears as a multiplet, rather than a simple singlet, with an apparent heptet structure, where the peaks are separated by 3.4 Hz at 400 MHz. This pattern persisted up to a temperature of 328 K in the $CHCl_3$ solution. This apparent multiplet is very odd since the expected ^{1}H NMR spectrum of chloroform in an isotropic solution is a singlet. Alternatively, one would have to assume that for some reason the residual coupling between the proton and the quadrupolar chloride nuclei in the $CHCl_3$ molecule became apparent.[11]

To examine whether this signal is indeed, as it appears, a multiplet and not a series of singlets, we performed several NMR experiments. First, we repeated the ^{1}H NMR spectrum of this sample on three different NMR spectrometers, with different magnetic fields of 4.7 T (200 MHz), 9.4 T (400 MHz), and 11.7 T (500 MHz). The obtained spectra of the encapsulated chloroform molecules are shown in Figure 3.

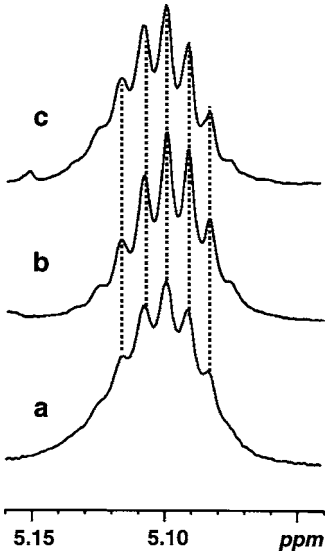

Figure 3. The ^{1}H NMR signals of the encapsulated chloroform molecules in a 20 mM $CHCl_3$ solution of **1b** (298 K) as obtained from three different NMR spectrometers: (a) 4.7 T (200 MHz), (b) 9.4 T (400 MHz), and (c) 11.7 T (500 MHz).

Spin−spin couplings are independent of the strength of the external magnetic field of the NMR spectrometer. Therefore, the splitting should remain constant (in hertz units) in NMR spectrometers with different external fields. However, this was not the case. It was found that the apparent

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(10) Diffusion NMR has become an important analytical tool for the characterization of chemical and supramolecular systems in solution. See, for example: (a) Pregosin, P. S.; Kummer, P. G. A.; Fermández, I. *Chem. Rev.* **2005**, *105*, 2977−2998. (b) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520−554.

(11) In the few examples, in which $^2J_{H^{35}Cl}$ or $^2J_{H^{37}Cl}$ was estimated, values which are 3−4 Hz were found. See, for example: Lindman, B.; Forsén, S. In *NMR Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; Springer-Verlag: Berlin, Heidelberg, New York, 1976; p 95.

"splittings" increased with the increase in the magnetic field strength of the NMR spectrometers. This apparent splitting was 1.7, 3.4, and 4.3 Hz for the 4.7 T (200 MHz), 9.4 T (400 MHz), and 11.7 T (500 MHz) spectrometers, respectively, implying that this signal is not a coupled multiplet, but rather several singlets. To further examine this signal, we performed a series of Hahn spin−echo experiments with different echo times. If a signal in the spectrum is a *J*-coupled multiplet, there should be a *J*-modulation as a function of the echo time. Changing the echo time in a Hahn spin−echo experiment should not affect noncoupled singlets, and they should remain the same.

Indeed, while all of the multiplets in the spectrum of **1b** were changed, the signal at 5.1 ppm remained the same for all the echo times used. These results support the conclusion that the signal of the encapsulated chloroform molecules is a series of singlets rather than a single *J*-coupled multiplet. Apparently, the chloroform molecules are trapped in slightly different molecular capsules, which are similar in their molecular weights (since the diffusion coefficients indicate formations of hexamers). It should be noted that there are six components in the hexamer, and if each component can be in two different arrangements, one should expect a heptet pattern.

Next, we examined the ^{1}H NMR spectra of **1b** in C_6H_6. When **1b** was dissolved in C_6H_6 rather than C_6D_6, an additional signal at about 5.5 ppm was observed. Again, this signal was found to have the same diffusion coefficient as that of **1b** in benzene within experimental errors ($0.21 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}, 20 mM, 298 K) and therefore was attributed to encapsulated benzene molecules. From integration of the ^{1}H NMR peaks, we concluded that the hexamer contains about 6 molecules of benzene in its cavity. In addition, we examined the relative affinity of chloroform and benzene molecules toward the cavity of the molecular capsule of **1b**. Figure 4 shows the signals of the encapsulated solvent molecules when **1b** was dissolved in $CHCl_3$ (Figure 4a), C_6H_6 (Figure 4b), and a 1:1 mixture of $CHCl_3$:C_6H_6 (Figure 4c).

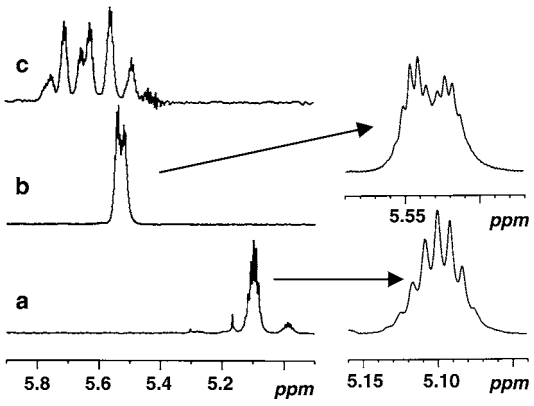

Figure 4. Section of the ^{1}H NMR spectra of **1b** (20 mM, 400 MHz, 298 K) showing the peaks of the encapsulated solvent molecules for solutions of $CHCl_3$ (a), C_6H_6 (b), and a 1:1 mixture of $CHCl_3$:C_6H_6 (c).

Again, the signals in the range of 5.4−5.8 ppm, shown in Figure 4c, were found to have the same diffusion coefficient ($0.21 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}, 20 mM, 298 K) as that of **1b** within experimental errors. When one mixes two equal amounts of two different solvents, one should expect at least some of the molecular capsules to contain only one of the two solvents. However, this was not the case for the hexameric capsule of **1b**. The spectrum of the hexameric capsule of **1b** in a 1:1 mixture of benzene and chloroform molecules (Figure 4c) shows no indication of hexameric capsules containing only chloroform (Figure 4a) or benzene (Figure 4b) molecules. Only new peaks were observed for the encapsulated solvent molecules, indicating that co-encapsulation of $CHCl_3$ and C_6H_6 is favored in the hexameric capsule of **1b**. To further examine this assumption, we prepared several samples of **1b** in different mixtures of $CHCl_3$:C_6H_6. Sections of the ^{1}H NMR spectra showing the signals of encapsulated solvent molecules are shown in Figure 5.

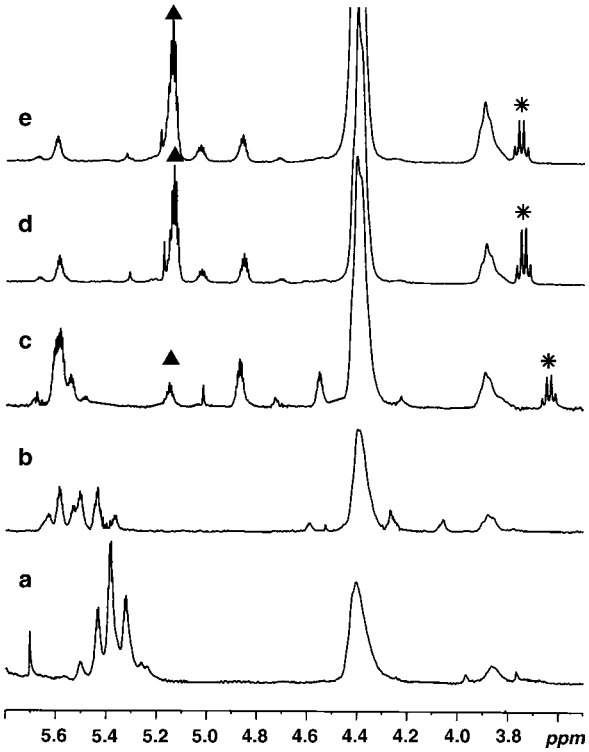

Figure 5. Section of the ^{1}H NMR spectra of **1b** (20 mM, 400 MHz, 298 K) in different mixtures of $CHCl_3$:C_6H_6 with the following ratios: (a) 1:10, (b) 1:1, (c) 10:1, (d) 50:1, and (e) 80:1. The ▲ symbol represents the peaks assigned to encapsulated chloroform, where there is no co-encapsulation. The ∗ symbol represents impurities in $CHCl_3$.

Figure 5a demonstrates that, even when there is a large excess of benzene, most of the benzene molecules remain co-encapsulated with chloroform molecules, and the signal

of pure encapsulated benzene is hardly seen (compare Figure 5a with Figure 4b). The same behavior was found for the chloroform molecules. When the ratio of $CHCl_3$:C_6H_6 is 10:1, only a small signal, which represents encapsulated chloroform with no co-encapsulation of benzene molecules, is observed (see ▲ in Figure 5c). At this chloroform/benzene ratio, most of the chloroform molecules are co-encapsulated with benzene molecules. Even when there is a larger excess of chloroform (80:1, Figure 5e), there are still signals of chloroform molecules co-encapsulated with benzene.

To further identify which peaks represent encapsulated chloroform or benzene molecules, we repeated the titration experiment for **1b** in $CHCl_3/C_6H_6$, $CDCl_3/C_6H_6$, and $CHCl_3/C_6D_6$ mixtures. For example, the peaks of the encapsulated solvent molecules for the three mixtures when the chloroform/benzene ratio was 10:1 are shown in Figure 6.

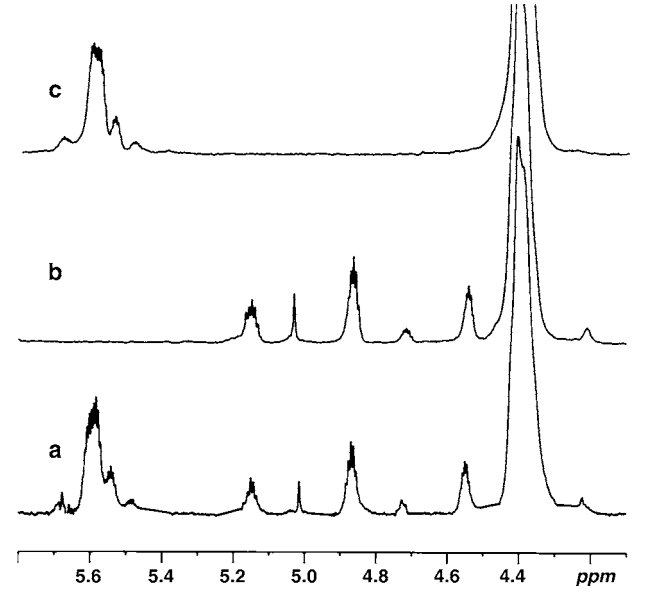

Figure 6. Section of the ^{1}H NMR spectra of **1b** (20 mM, 400 MHz, 298 K) in a 10:1 mixture of chloroform:benzene, where (a) is a mixture of $CHCl_3/C_6H_6$, (b) a mixture of $CHCl_3/C_6D_6$, and (c) a mixture of $CDCl_3/C_6H_6$.

From these experiments, we unequivocally identified the peaks that represent chloroform co-encapsulated with benzene and vice versa. The difference between the chemical shifts of the encapsulated chloroform (co-encapsulated with benzene) and that of benzene (co-encapsulated with chloroform) as compared with those of nonencapsulated solvents, both in the presence and absence of the hexameric capsule of **1b**, is depicted in Figure 7. Interestingly, we found that

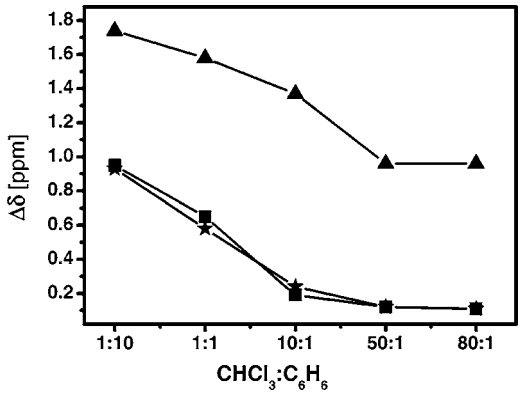

Figure 7. The difference in the chemical shifts of the encapsulated chloroform and benzene (▲) as compared with those of nonencapsulated solvents both in the presence (★) and absence of the hexameric capsule of **1b** (■).

the differences for the encapsulated peaks are much larger. It seems that the excessive high-field shift of the encapsulated chloroform molecules co-encapsulated with benzene is due to the aromatic solvent-induced shift (ASIS) phenomenon, which is enhanced for encapsulated molecules. The reason may be the close proximity of the co-encapsulated molecules in the capsules and, more importantly, the larger molecular fraction of the so-called chloroform−benzene complex in the capsules as compared with the bulk.

In conclusion, we demonstrated that although the signal of the encapsulated chloroform molecules in the capsules of **1b** appears as a multiplet it is in fact a series of different singlets, as deduced by NMR techniques. The same behavior is observed for the encapsulated benzene molecules. In addition, we showed that chloroform and benzene co-encapsulation is preferred, and that the close proximity and the larger molecular fraction of the chloroform/benzene complex in the capsule is manifested by an overexpression of the ASIS effect.

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