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The Effect of Alcohol Structures on the Interaction Mode with the Hexameric Capsule of Resorcin[4]arene

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Abstract: After more than a century of research on resorcin[4]arenes (**1**) it is clear that such systems form spontaneously [$\mathbf{1}_6(H_2O)_8$]-type hexameric capsules in wet, non-polar, organic solvents. However, the interactions of these hexameric capsules with alcohols are far from being solved. Here we provide the results of an extensive study on the interaction of different alcohols with the hexameric capsules of resorcin[4]arene **1a** by focusing on the exchange of magnetization manifested in diffusion NMR measurements of such capsular systems. We found that some alcohols such as 2-octyl-1-dodecanol and 1-octadecanol do not interact with the hexamers of **1a**, whereas other alcohols such as 3-ethyl-3-pentanol, 2-ethyl-1-butanol and more act as simple guests and are simply encapsulated in the hexamers. Others alcohols such as 3-pentanol, 2-methyl-1-butanol and others, are part of the hexameric structure where they can exchange magnetization with alcohols in the bulk. The bulkier alcohols, due to an increase of the chain length or in branching, have a higher tendency to be encapsulated rather than being part of the hexameric capsule superstructure. This study demonstrate the unique information that diffusion NMR spectroscopy can provide on supramolecular systems in solution and on the precaution that should be exercised when analyzing diffusion NMR data of such dynamic supramolecular capsules.

Keywords: hexamers · hydrogen bonds · molecular capsules · NMR spectroscopy · resorcinarenes · supramolecular chemistry

Introduction

Molecular capsules in general[1] and self-assembled molecular capsules held together by different intermolecular interactions in particular, have received considerable attention in the past two decades.[2] Hydrogen bonds were extensively used to construct both dimeric[3] and hexameric supramolecular capsules.[4–6] As the structure of such capsules became more and more complex it is clear that characterization of such dynamic systems in solution call for the use of additional spectroscopic and analytical methods. Indeed in recent years, diffusion NMR spectroscopy[7] was found to be an effective method for studying supramolecular systems in solution[8] and for monitoring, for example, the structure, stability, and self-sorting of hydrogen-bonded molecular capsules.[9,10] By using diffusion NMR spectroscopy, it was demonstrated that molecules such as resorcin[4]arene **1a** self-assemble spontaneously to form hexameric capsules in wet organic solvents, without the addition of a specific guest by encapsulating solvent molecules.[5e,10a,b] In such hexameric capsules water molecules play a unique role. It was found that eight water molecules participate in the formation of the hexameric capsules of resorcin[4]arenes like **1a**.[10a,b] These water molecules are in fast exchange on the ^{1}H NMR time scale with the bulk water in the solution.[10a,b,11] Interestingly, water molecules have no effect on the formation of hexameric capsules of **1d** and **1e** that form $\mathbf{1d}_6$- and $\mathbf{1e}_6$-type capsules both in solution and in the solid state.[4b,5c,f,10b,12] The resemblance of water molecules to alcohol molecules raised the question whether alcohols can replace water molecules in the hexameric structure of **1a**. Early reports investigating the interaction between **1a** and different alcohols were reported by Aoyama and co-workers during the 1990s.[13] There they proposed 1:1 complexes between **1a** and different alcohols, years before the hexameric capsules were identified. In 2006, Ugono and Holman reported the solid-state structure of the hexameric capsules of **1c**, in which six of the eight water molecules were replaced by six 2-ethyl-1-hexanol (**6**) molecules.[14] Subsequently, Mattay and co-workers used diffusion NMR spectroscopy to probe the self-assembly of **1a** in the presence of various alcohols in dry chloroform solutions and suggested that different species were obtained when different alcohols were used.[15] Very recently, we have shown, by using diffusion NMR spectroscopy, that high-field peaks in the ^{1}H NMR spectrum of the alcohol guests in the presence of the hexameric capsules of **1a** do not necessarily imply guest encapsulation within the capsule.[16] We have shown that despite the similar ^{1}H NMR spectra of different alcohols in the presence of **1a**, 2-ethyl-butanol (**5**) and 2-ethyl-hexanol (**6**) are encapsulated in the

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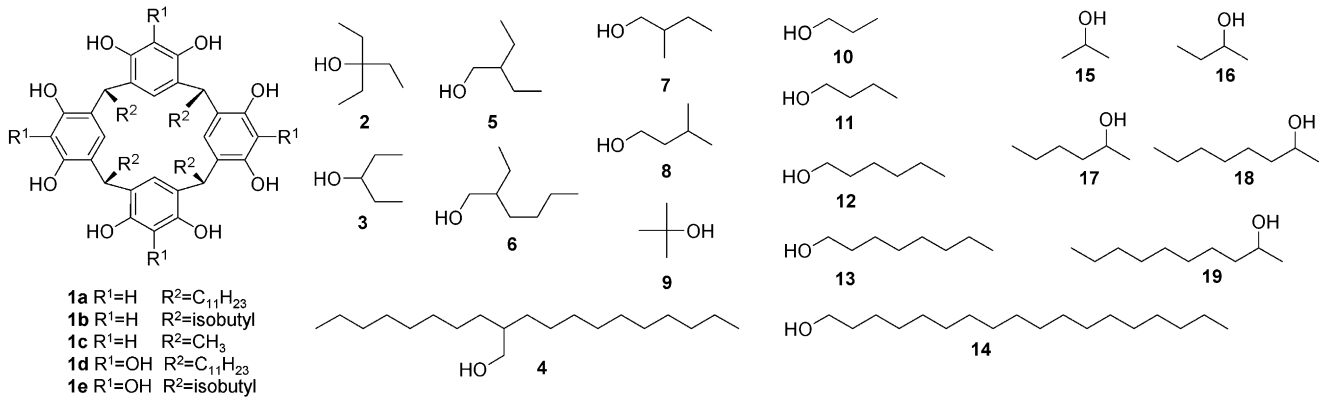
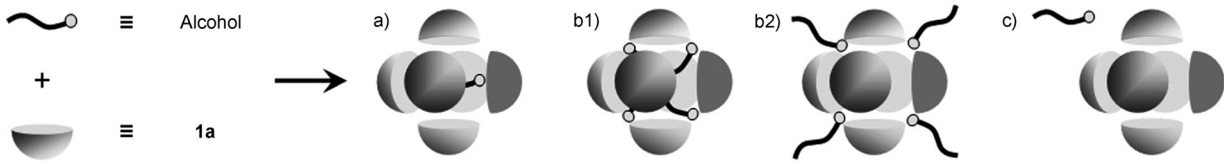


Scheme 1. The structures of resorcin[4]arene (**1a**–**c**) pyrogallolarene (**1d**,**e**), 3-ethyl-3-pentanol (**2**), 3-pentanol (**3**), 2-octyl-1-dodecanol (**4**), 2-ethyl-1-butanol (**5**), 2-ethyl-1-hexanol (**6**), 2-methyl-1-butanol (**7**), 3-methyl-1-butanol (**8**), *tert*-butanol (**9**), 1-propanol (**10**), 1-butanol (**11**), 1-hexanol (**12**), 1-octanol (**13**), 1-octadecanol (**14**), 2-propanol (**15**), 2-butanol (**16**), 2-hexanol (**17**), 2-octanol (**18**), and 2-decanol (**19**).



Scheme 2. Possible sites that an alcohol can occupy in a solution of the hexameric capsule of **1a**.

hexamers of **1a**, whereas 2-butanol (**16**) and 2-hexanol (**17**) replace some of the water molecules in the hexameric structure of the capsules. It was found that alcohols that are part of the capsule network and that are not encapsulated can exchange magnetization with alcohol molecules in the bulk solution.[16] There it was shown that by measuring the diffusion of such complexes with the longitudinal eddy current delay (LED)[17] sequence with different echo time delays (t_es; see Figure S1 in the Supporting Information for the LED pulse sequence), one can identify which of the alcohols are encapsulated and which are located on the surface of the capsule.[16]

In the present paper, we aimed at evaluating the generality of these peculiar findings. Therefore we studied the interaction of the hexameric capsule of **1a** with a large series of alcohols (see Scheme 1) by using diffusion NMR spectroscopy at various t_es. We show that different alcohols behave differently. We found that the exchange of magnetization of the alcohols depends on the size and branching of the alcohols. More bulkier and branched alcohols show less exchange of magnetization and are encapsulated, others are part of the structure of the hexameric capsules, whereas very large alcohols show no interaction with the hexameric capsule of **1a**.

Results and Discussion

Alcohols in a solution of the hexameric capsule of **1a** can, in principle, accommodate three main locations (Scheme 2). Alcohols can be encapsulated (Scheme 2a), can be part of the hexameric structure (Scheme 2b), or can be in the bulk (Scheme 2c).

Figure 1 shows the ^{1}H NMR spectra of a slightly acidified $CDCl_3$ solution of **1a** in the presence of three different alcohols, namely 3-ethyl-3-pentanol (**2**), 3-pentanol (**3**), and 2-octyl-1-dodecanol (**4**). Addition of ten equivalents of **2** to the $CDCl_3$ solution of **1a** afforded the ^{1}H NMR spectrum shown in Figure 1a. In this ^{1}H NMR spectrum new peaks of **2** are observed in the high-field region. Addition of **3** to the $CDCl_3$ solution of **1a** also afforded a spectrum with high-field peaks as shown in Figure 1b. According to our previous results such high-field peaks can represent "bound" alcohol molecules, which are encapsulated within the hexame-

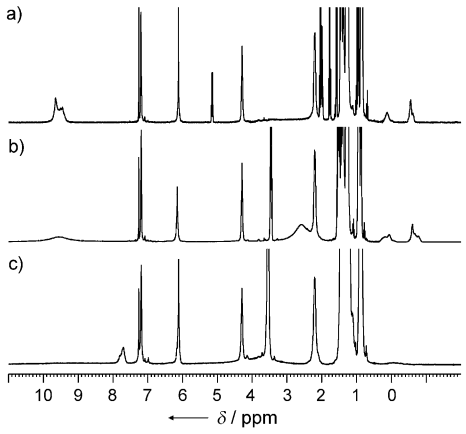


Figure 1. ^{1}H NMR spectra (400 MHz, 298 K) of a solution of **1a** in $CDCl_3$ (25 mM) in the presence of a) **2**, b) **3**, and c) **4** (250 mM each).

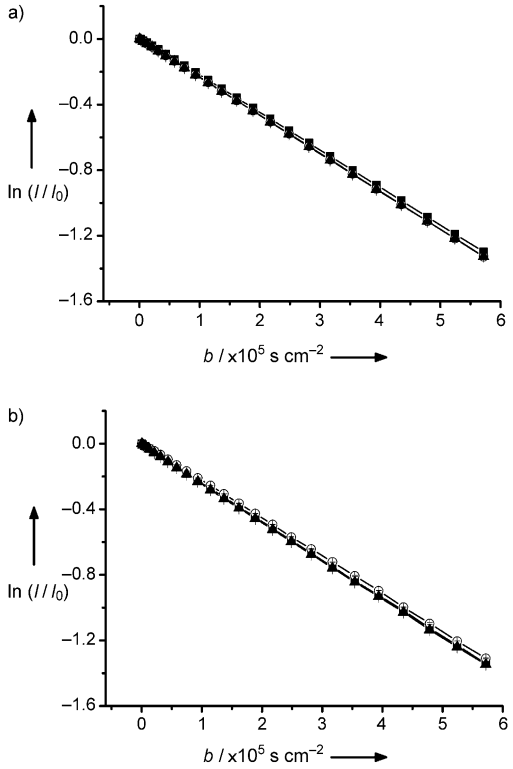


Figure 2. Natural logarithm of the normalized signal decay ($\ln(I/I_0)$) as a function of the b value (see the Experimental Section for the definition of b, 400 MHz, 298 K) for one of the peaks of a) **1a** and b) "bound" **2** in $CDCl_3$ as extracted from the LED sequence with different t_es of 5 (■), 50 (○), and 150 ms (▲).

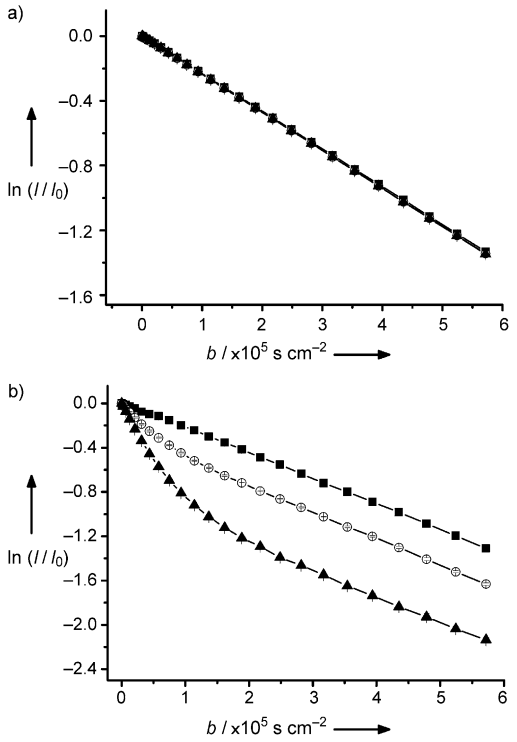


Figure 3. Natural logarithm of the normalized signal decay ($\ln(I/I_0)$) as a function of the b value (400 MHz, 298 K) for one of the peaks of a) **1a** and b) "bound" **3** in $CDCl_3$ as extracted from the LED sequence with different t_es of 5 (■), 50 (○), and 150 ms (▲).

ric capsule of **1a** or alcohol molecules, which are part of the hexameric capsule.[16]

To determine what these high-field peaks represent, we measured the signal decay of these high-field-shifted "bound" alcohol peaks and the peaks of **1a**, by the LED diffusion sequence at different t_es. We performed such experiments because we have shown that diffusion measurements performed with the LED sequence at long t_e allow the exchange of magnetization to affect the signal decay.[11] For the $CDCl_3$ solution of **2** in the presence of **1a** the signal decay for the two species in the sample (**1a** and "bound" **2**) was found to be mono-exponential and the same at all sampled t_e values (see Figure 2 and Figure S2 in the Supporting Information). The extracted diffusion coefficient for **1a** and **2** was $(0.23\pm0.01)\times10^{-5}\ cm^2\,s^{-1}$. These results imply that **2** is encapsulated in the hexameric capsule of **1a** under the experimental conditions used. Figure 1c shows the ^1H NMR spectrum of **1a** in the presence **4**. No additional high-field peaks are observed, which indicates that **4** is not encapsulated and is not part of the network of the hexameric capsule of **1a**.

When we measured the signal decay of the high-field peaks of "bound" **3** (shown in Figure 1b) and the peaks of **1a** for the **1a**/**3** $CDCl_3$ solution we found that the signal decay of the peaks of **1a** is mono-exponential and is not affected by an increase in t_e (see Figure 3 and Figure S3d–f in the Supporting Information). However, the signal decay of "bound" **3** was found to be dramatically affected by the change in t_e and became bi-exponential at long t_e. As t_e was increased, the slow component gradually disappeared and the fast component became more predominant (see Figure 3 and Figure S3a–c in the Supporting Information). On the basis of these results and our previous observations[16] we could conclude that the high-field peaks of "bound" **3** are not that of encapsulated guest molecules but rather represent molecules of **3** that are part of the superstructure of the hexameric capsule of **1a**.

After establishing that, we have a quick mean to characterize the alcohol location in the presence of the hexameric capsules of **1a**; we explored whether there is any way we can predict the alcohols behavior according to the structure of the alcohol. For doing that we first recorded the ^1H NMR spectra of alcohols **2**–**19** in the $CDCl_3$ solution of the hexamer of **1a** (Figure S4 in the Supporting Information). Then, in the cases where high-field peaks were observed, we measured the signal decay of these peaks at different t_es, by using the LED diffusion sequence. According to our results, alcohols **2**, **5**, **6**, **13**, and **19** are truly encapsulated within the hexameric capsule of **1a**, whereas alcohols **3**, **7**, **8**, **9**, **11**, **12**, and **15**–**18** are primarily part of the hexameric structure of

1a. Alcohols **4**, **10**, and **14** show no interaction with the hexameric capsule of **1a**. Alcohols **4** and **14** seem to be too large to be encapsulated or to be part of the hexameric capsule, whereas alcohol **10** seems to be too small. The signal decay of the peaks of alcohol **4** in $CDCl_3$ solutions both in the presence and absence of **1a** were found to be the same (see Figure S5 in the Supporting Information), indicating that **4** does not interact with the external faces of the hexameric capsule of **1a**. The same result was obtained for the solution of alcohol **14** in the presence of **1a** (see Figure S6 in the Supporting Information). This is in contrast to what was recently found for large trialkylamines and tetraalkylammonium salts in the presence of the hexameric capsule of **1a**.[10e] For alcohols **2**, **5**, **6**, **13**, and **19** the branching and the size of the alcohols do not allow them to participate in the supramolecular assembly of the hexameric structure of **1a**, but they still can be encapsulated within the hexamer of **1a**. The more interesting group, however, are alcohols **3**, **7**–**9**, **11**, **12**, **15**–**18**, which are small enough or have limited branching that allow them to be part of the hexameric capsule of **1a**. These alcohols can exchange magnetization with the alcohols in the bulk.

The next step was to qualitatively compare the relative extent of the exchange of various alcohols in the presence of the hexameric capsule of **1a**. To this end, we monitored the signal decay of the high-field peaks of different alcohols at $t_e = 150$ ms, where the exchange is particularly pronounced (see Figures S7–S10 in the Supporting Information). Alcohols **10**–**14** are linear, unbranched alcohols of different chain length. As mentioned before, alcohols **10** and **14** show no high-field peaks in the presence of the hexameric capsule of **1a**. Figure 4 shows the signal decay of the high-field peaks of alcohols **11**–**13** for $t_e = 150$ ms. The extracted apparent diffusion coefficients (ADC) for these *n*-alcohols were found to be (2.04 ± 0.01), (0.41 ± 0.01), and $(0.25 \pm 0.01) \times 10^{-5}\ cm^2 s^{-1}$ for **11**–**13**, respectively. For alcohol **13** the signal decay is mono-exponential and is not affected by a change in t_e. For alcohol **12** the signal decay is bi-exponential and we sampled both a slow and fast component. For alcohol **11** only the fast component was observed

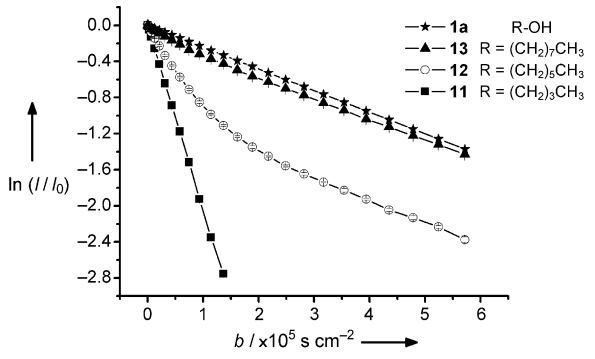


Figure 4. Natural logarithm of the normalized signal decay ($\ln(I/I_0)$) as a function of the *b* value (400 MHz, 298 K) for the peak of **1a** (★), "bound" **11** (■),"bound" **12** (○), and "bound" **13** (▲) of the $CDCl_3$ solution of **1a** in the presence of the different alcohols **11**–**13** as extracted from the LED sequence with $t_e = 150$ ms.

at this relatively long t_e. These results show that the length of the chain of the guest alcohol affects the extent of exchange. The shorter the alcohol is, the faster is the exchange, and the larger is the fast diffusing component of the signal decay observed at $t_e = 150$ ms. The exchange is more pronounced for alcohol **11** as compared to alcohol **12**, which in turn exchange magnetization faster than alcohol **13**, which is in fact encapsulated within the hexameric capsule of **1a**.

For alcohols **15**–**19**, which are all 2-ols of different chain length, the extracted apparent diffusion coefficients were (2.37 ± 0.01), (2.01 ± 0.02), (0.38 ± 0.01), (0.27 ± 0.01), and $(0.23 \pm 0.01) \times 10^{-5}\ cm^2 s^{-1}$, respectively when measured with the LED sequence with a t_e of 150 ms. The signal decays for these alcohols in the presence of **1a** are presented in Figure 5 showing again that the fast component becomes

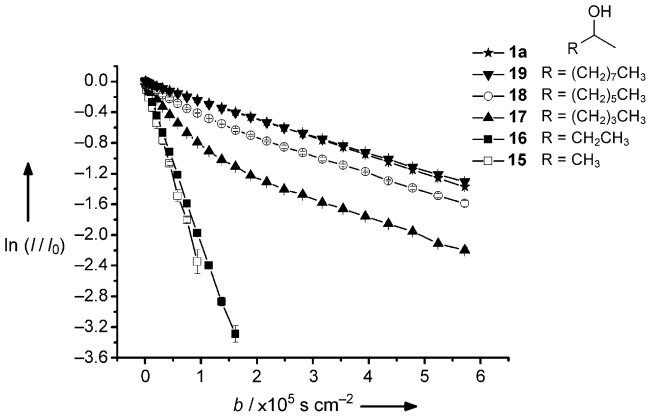


Figure 5. Natural logarithm of the normalized signal decay ($\ln(I/I_0)$) as a function of the *b* value (400 MHz, 298 K) for the peak of **1a** (★), "bound" **15** (□), "bound" **16** (■),"bound" **17** (▲),"bound" **18** (○), and "bound" **19** (▼), of the $CDCl_3$ solution of **1a** in the presence of the different alcohols **15**–**19** as extracted from the LED sequence with $t_e = 150$ ms.

more predominate as the chain length decreases. Thus, for the shortest alcohols **15** and **16** the exchange was faster than for the longer alcohol **17**, which in turn showed a faster exchange than alcohols **18** and **19**. Alcohol **19** is in fact encapsulated in the hexameric capsule of **1a** and does not exchange magnetization with the alcohol molecules in the bulk even at $t_e = 150$ ms.

The results for alcohols with more branching are plotted in Figure 6. Indeed, alcohols **5**–**8** have a butanol chain with different branching sites, whereas alcohol **11** is the unbranched 1-butanol. We found that for alcohols **5** and **6** the signal decay was mono-exponential, not affected by t_e, and the obtained diffusion coefficient was $(0.23 \pm 0.01) \times 10^{-5}\ cm^2 s^{-1}$, exactly the same as that the one of the hexamers of **1a** in the same solution. The signal decays of alcohols **7**, **8**, and **11** were bi-exponential and their ADCs were found to be (0.47 ± 0.01), (0.67 ± 0.01), and $(2.04 \pm 0.01) \times 10^{-5}\ cm^2 s^{-1}$, respectively. Alcohols **5** and **6** are the most branched alcohols in this series and were found to be encapsulated in the hexameric capsule of **1a**. Alcohols **7** and **8**

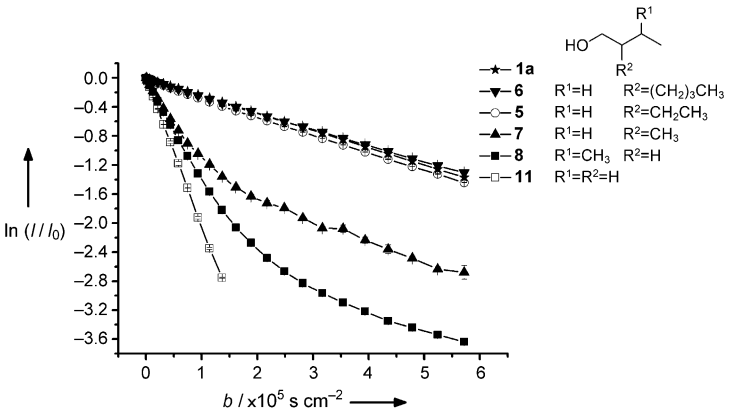


Figure 6. Natural logarithm of the normalized signal decay ($\ln(I/I_0)$) as a function of the b value (400 MHz, 298 K) for the peak of **1a** (★), "bound" **6** (▼),"bound" **5** (○), "bound" **7** (▲), "bound" **8** (■), and "bound" **11** (□) of the $CDCl_3$ solution of **1a** in the presence of the different alcohols **6**, **5**, **7**, **8**, and **11** as extracted from the LED sequence with $t_e = 150$ ms.

show a bi-exponential signal decay at $t_e = 150$ ms and seem to participate in the hexameric capsule formation. They differ from each other in the methyl group location. The signal decay of alcohol **11** (1-butanol) shows only a fast component at $t_e = 150$ ms as expected for an unbranched alcohol.

A similar trend was observed in Figure 7. Figure 7 presents the signal decays of the high-field peaks of the alcohols **2**, **3**, and **9**, and of the reference alcohol **15** in the presence

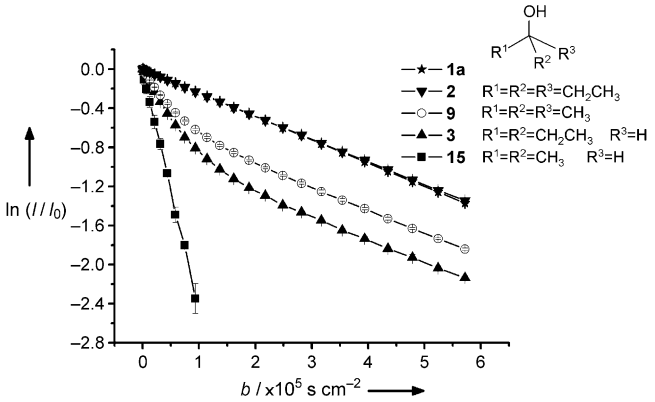


Figure 7. Natural logarithm of the normalized signal decay ($\ln(I/I_0)$) as a function of the b value (400 MHz, 298 K) for the peak of **1a** (★), "bound" **2** (▼), "bound" **9** (○), "bound" **3** (▲), and "bound" **15** (■) of the $CDCl_3$ solution of **1a** in the presence the different alcohols **2**, **9**, **3**, and **15** as extracted from the LED sequence with $t_e = 150$ ms.

of the hexamer of **1a**. For alcohol **2** the obtained signal decay was mono-exponential even at the long t_e of 150 ms, which indicates that alcohol **2** is encapsulated within the hexameric capsule. The signal decay of alcohols **3** and **9** were found to be bi-exponential with ADCs of (0.37 ± 0.01) and $(0.31 \pm 0.01) \times 10^{-5}\ cm^2 s^{-1}$, respectively. Alcohol **15** has a mono-exponential signal decay with a high ADC of $(2.37 \pm 0.01) \times 10^{-5}\ cm^2 s^{-1}$, as expected.

All these results show that the structure of the alcohol has a profound effect on the nature of the interaction of the alcohols with the hexameric capsule of **1a** in chloroform solution. Although we could not find a quantitative correlation between the exchange rate and a single parameter of the alcohols studied, clearly we found, qualitatively, that the longer and/or more branched the alcohols are, the higher their tendency to be encapsulated is. The more bulky alcohols have a lower tendency to replace the water molecules in the hexameric capsules of **1a**. Regarding the mechanism it may well be that, as suggested by one of the referees, all alcohols are first encapsulated and only those alcohols with the higher affinity can then replace the water molecules, which occupy the surface of the hexameric capsules of the resorcin[4]arene. A series of competition experiments are under way to try to resolve this issue and those will be reported once conclusive data will be obtained.

Conclusion

We explored the interaction of different alcohols **2**–**19** with the hexameric capsule of **1a** in wet $CDCl_3$ solution and mapped the alcohols location according to the ^1H NMR spectra and diffusion NMR measurements. We have shown that the location of the alcohols depends on their structure. Large alcohols, such as **4** and **14**, or small alcohol, such as **10**, show no interaction with the hexameric capsule of **1a**. Alcohols such as **2**, **5**, **6**, **13**, and **19** have an appropriate structure suitable for guest encapsulation within the hexameric capsule of **1a**. Alcohols **3**, **7**–**9**, **11**, **12**, and **15**–**18** that have relatively short and/or unbranched structures tend to be part of the hexameric capsule of **1a** and seem to replace some of the water molecules in the hexameric capsule of **1a**. These alcohols can exchange magnetization with the alcohols in the bulk on the time scale of our diffusion experiments.

Experimental Section

General experimental details: Diffusion NMR measurements were carried out on a 400 MHz Avance Bruker NMR spectrometer equipped with a z-gradient system capable of producing a maximal pulse gradient of about 50 gauss cm^{-1} in the z direction. These diffusion experiments were performed by using a 5 mm inverse probe and a longitudinal eddy currents diffusion (LED) sequence.[17] Sine-shaped pulse gradients, with a duration of 4 ms were incremented from 0.7–32.2 gauss cm^{-1} in 24 steps, and the pulse gradient separation was set to 50 ms. The t_e effect was measured with different t_es of 5, 50, and 150 ms. For the diffusion measurements, the samples were placed in 4 mm NMR tubes that were then placed coaxially in 5 mm NMR tubes, which act as a thermal insulating system and increase the accuracy and reproducibility of the diffusion measurements by reducing the chance of convections in the sample. The diffusion coefficients were extracted from Equation (1):[17]

$$\ln(I/I_0) = -\gamma^2\delta^2G^2(2/\pi)^2(\Delta-\delta/4)D = -bD \quad (1)$$

where I and I_0 are the echo intensity, in the presence and absence of the gradient pulse, respectively, γ is the gyromagnetic ratio, G is the pulse gradient strength, $2/\pi$ is a geometrical correction factor due to the sine shape of the pulse gradients used, δ is the duration of the pulse gradient, Δ is the time interval between the leading edges of the pulse gradient used, and D is the diffusion coefficient. The diffusion coefficients were extracted from the slope of the plot of $\ln(I/I_0)$ versus the b value. All diffusion NMR data were acquired at 298 K and were obtained in triplicate. The given values represent means $\pm$ the standard deviation of the means.

Materials: All starting materials, guest molecules, reagents, and the deuterated solvents ($CDCl_3$, DCl) were purchased from Aldrich (Milwaukee, WI) and were used as supplied. Compound **1a** was prepared according to modifications of the previously published procedure.[18]

Acknowledgements

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