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## Self-Recognition, Structure, Stability, and Guest Affinity of Pyrogallol[4]arene and Resorcin[4]arene Capsules in Solution

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**Abstract:** In the present study, we used diffusion NMR to probe the structures and characteristics of the products obtained from the self-assembly of resorcin[4]arenes **1a** and **1b** and pyrogallol[4]arenes **2a** and **2b** in CDCl<sub>3</sub> solutions. It was found that all four molecules self-assemble into hexameric capsules. The hexameric capsules of pyrogallol[4]arenes **2a** and **2b** were found to be more stable than the capsules of resorcin[4]arenes **1a** and **1b** in polar media. We also studied the role of water molecules in the self-assembly of the different capsules and found that water molecules are part of the hexameric capsules of resorcin[4]arenes **1a** and **1b** but not in the capsules of pyrogallol[4]arenes **2a** and **2b**. It was found that the self-assembly process between the resorcin[4]arenes and pyrogallol[4]arenes proceeds with self-recognition. When mixing two macrocycles of different types in a chloroform solution, no heterohexamers are formed, only the capsule constructed from the same macrocycle is detected. However, when two resorcin[4]arenes (i.e., **1a** and **1b**) or two pyrogallol[4]arenes (i.e., **2a** and **2b**) are mixed, heterohexamers are formed over time. In addition, we found that resorcin[4]arenes and pyrogallol[4]arenes differ significantly in their guest affinity. The capsules of **1a** and **1b** can accommodate both the tertiary alkylamines and their respective ammonium salts, while the capsules of **2a** and **2b** encapsulate only the neutral tertiary alkylamines.

### Introduction

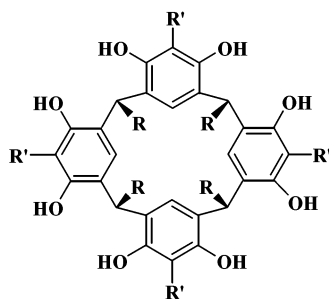
Self-assembly is a process of unique importance both in biological and chemical systems.<sup>1</sup> Container molecules and molecular capsules, an intriguing class of compounds, were obtained by both covalent binding and self-assembly through noncovalent interactions.<sup>2,3</sup> The latter process may result in a reversible encapsulation of different chemical species (i.e., guests) in the formed self-assembled molecular capsules. Different noncovalent self-assembled molecular capsules based on metal–ligand interactions, hydrogen bonds, and electrostatic interactions were prepared and studied over the past decade.<sup>3</sup> Among these self-assembled molecular capsules, calixarenes and resorcinarenes were studied extensively.<sup>4–6</sup> The interest in the

self-assembled molecular capsules stems from their ability to isolate the encapsulated guests from the bulk. These molecular capsules were shown to be capable of enantioselective recognition,<sup>7</sup> isolation, and stabilization of reactive species.<sup>8</sup> They were also used to catalyze reactions within their cavities.<sup>9</sup> Most of the molecular capsules prepared to date were of dimeric nature and were prepared by Rebek and Böhmer's groups.<sup>4–6</sup> These molecular capsules afford a new type of isomerism that was termed constellation isomerism.<sup>10</sup>

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Chart 1



- 1a** R=isobutyl R'=H      **2a** R=isobutyl R'=OH  
**1b** R= C<sub>11</sub>H<sub>23</sub> R'=H      **2b** R= C<sub>11</sub>H<sub>23</sub> R'=OH  
**1c** R=CH<sub>3</sub> R'=H

Atwood and co-workers have shown, in a pioneering article, that [c]-methyl resorcin[4]arene (**1c**) (Chart 1) forms a hexameric capsule with eight water molecules in the solid state.<sup>11a</sup> Subsequently, Rebek and Shivanyuk demonstrated that **1b** forms a stable hexameric capsule in a water-saturated chloroform solution in the presence of suitable guests such as tetrahexylammonium bromide and covalent tetrabutylantimony(v) bromide Bu<sub>4</sub>SbBr.<sup>11b,c</sup> Mattay's group demonstrated that **2a** also forms a hexameric capsule in the solid state.<sup>12a</sup> Atwood and co-workers subsequently prepared this and related molecular capsules and claimed that they appear to be stable even in polar solvents.<sup>12b,c</sup>

In recent years, diffusion NMR<sup>13</sup> was used to probe complexation of different complexes and evaluate their association constants.<sup>14a–d</sup> Diffusion NMR was also used to study ion-pairing aggregation,<sup>14e,f</sup> the structure of organometallic compounds,<sup>14g,h</sup> and other reactive intermediates.<sup>14i,j</sup> The formation of supramolecular systems such as pseudorotaxanes and catenanes was also probed with the aid of diffusion NMR.<sup>14k,l</sup> This technique was also used to characterize dendrimer generations<sup>14m</sup> and map the hydration sphere around crown ether and its complexes in organic solvents such as CDCl<sub>3</sub>.<sup>14n</sup> In addition, it was shown that diffusion NMR is a powerful tool for probing encapsulation.<sup>15</sup> We recently showed, using this technique, that

**1b** and **2b** self-assemble spontaneously into hexameric capsules of the [(**1b**)<sub>6</sub>(H<sub>2</sub>O)<sub>8</sub>]- and [(**2b**)<sub>6</sub>]-type, respectively, in CDCl<sub>3</sub> solutions.<sup>16a–c</sup>

Here, we present the comparative study of the products of the self-assembly processes of the two resorcin[4]arenes **1a** and **1b** and pyrogallol[4]arenes **2a** and **2b** in chloroform solutions using diffusion NMR. The emphasis of this study is on the comparison between the characteristics of the self-assembled molecular capsules, both within the macrocycle type and across the types of the macrocycles used. The nature and relative stability of the obtained molecular capsules were determined in addition to the role of water molecules. We also followed the self-recognition in the self-assembly processes of mixtures of all four macrocycles (**1a**, **1b**, **2a**, and **2b**) in solutions. In addition, the guest's affinity of these hydrogen bond hexameric capsules was investigated.

## Experimental Section

**General.** NMR diffusion measurements were performed on a 400 MHz Avance Bruker NMR spectrometer equipped with a Great1 gradient system capable of producing magnetic field pulse gradients in the z-direction of about 50 G cm<sup>-1</sup>. The diffusion experiments were performed using the stimulated echo diffusion sequence<sup>13b</sup> or the DOSY sequence.<sup>17</sup> All experiments were carried out using a 5-mm inverse probe. For the stimulated echo diffusion experiments, the rectangular pulsed gradients of 2 ms duration were incremented from 0 to 40.2 G cm<sup>-1</sup> in 10 steps, and the pulse gradient separation was 62 ms. For the LED experiments,<sup>17</sup> the sine shape pulsed gradients of 4 ms duration were incremented from 0.7 to 32.2 G cm<sup>-1</sup> in 10 steps, and the pulse gradient separation was 40 ms. All measurements were performed at least three times, and the reported diffusion coefficients are the mean ± standard deviation of three experiments. Only data where the correlation coefficients of ln(I/I<sub>0</sub>) versus γ<sup>2</sup>δ<sup>2</sup>g<sup>2</sup>(Δ-δ/3) were higher than 0.999 are reported. The measurements were all preformed at 298.0 K. All diffusion measurements were performed in a 4-mm NMR tube inserted in a 5-mm NMR tube.

**Materials.** All starting materials, guest molecules, reagents, and the deuterated solvents (CDCl<sub>3</sub>, CD<sub>3</sub>OD, and DCl) were purchased from Aldrich (U.S.A.) and used as supplied. Compounds **1a**, **1b**, **2a**, and **2b** were prepared according to modifications of the procedure published previously.<sup>18</sup>

The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic parameters of the obtained hexameric capsules in CDCl<sub>3</sub> solutions are given below.

<sup>1</sup>H NMR of [(**1a**)<sub>6</sub>(H<sub>2</sub>O)<sub>8</sub>] (400 MHz, CDCl<sub>3</sub>, 25 °C, 20 mM): δ = 9.52 (OH, broad, 48H), 7.20 (s, 24H), 6.14 (s, 24H), 4.44 (t, J = 7.4 Hz, 24H), 2.09 (m, 48H), 1.49 (m, 24H), 0.98 (t, J = 6.2 Hz, 144H).

<sup>13</sup>C{<sup>1</sup>H}NMR of [(**1a**)<sub>6</sub>(H<sub>2</sub>O)<sub>8</sub>] (100 MHz, CDCl<sub>3</sub>, 25 °C, 20 mM): δ = 151.27, 150.96, 125.60, 125.50, 124.86, 103.57, 42.78, 31.62, 26.81, 23.56, 23.35 ppm.

<sup>1</sup>H NMR of (**2a**)<sub>6</sub> (400 MHz, CDCl<sub>3</sub>, 25 °C, 20 mM): δ = 8.78 (s, 24H), 7.45 (s, 24H), 6.86 (s, 24H), 6.83 (s, 24H), 4.51 (t, J = 7.0 Hz, 24H), 2.12 (broad, 48H), 1.54 (m, 24H), 1.02 (broad, 144H).

<sup>13</sup>C{<sup>1</sup>H}NMR of (**2a**)<sub>6</sub> (100 MHz, CDCl<sub>3</sub>, 25 °C, 20 mM): δ = 139.14, 137.96, 132.08, 126.00, 124.68, 114.95, 42.65, 32.21, 26.90, 23.63, 23.23 ppm.

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**Table 1.** Diffusion Coefficients of **1a**, **1b**, **2a**, and **2b** in Chloroform Solutions at 298 K

system [ $M_w$ ] <sup>a</sup>	diffusion coefficients [ $\times 10^5 \text{ cm}^2 \text{ s}^{-1}$ ]			
	<b>1a</b> [712 g mol <sup>-1</sup> ]	<b>1b</b> [1104 g mol <sup>-1</sup> ]	<b>2a</b> [776 g mol <sup>-1</sup> ]	<b>2b</b> [1168 g mol <sup>-1</sup> ]
3mM CDCl <sub>3</sub>	0.34 $\pm$ 0.01	0.26 $\pm$ 0.01	0.36 $\pm$ 0.01	0.27 $\pm$ 0.01
+CD <sub>3</sub> OD	0.58 $\pm$ 0.01	0.44 $\pm$ 0.01	0.59 $\pm$ 0.01	0.45 $\pm$ 0.01
CHCl <sub>3</sub> <sup>c</sup>	0.33 $\pm$ 0.01	0.27 $\pm$ 0.01	0.33 $\pm$ 0.01	0.24 $\pm$ 0.01
	0.34 $\pm$ 0.01 <sup>b</sup>	0.27 $\pm$ 0.01 <sup>b</sup>	0.31 $\pm$ 0.01 <sup>b</sup>	0.24 $\pm$ 0.01 <sup>b</sup>

<sup>a</sup> Molecular weights of the monomers. <sup>b</sup> The diffusion coefficient of the encapsulated chloroform molecules. <sup>c</sup> The macrocycles' concentrations were 20, 15, 20 and 27 mM for **1a**, **1b**, **2a**, and **2b**, respectively.

<sup>1</sup>H NMR of [(**1b**)<sub>6</sub>(H<sub>2</sub>O)<sub>8</sub>] (400 MHz, CDCl<sub>3</sub>, 25 °C, 65 mM):  $\delta$  = 9.52 (OH, broad, 48H), 7.21 (s, 24H), 6.12 (s, 24H), 4.30 (t,  $J$  = 7.0 Hz, 24H), 2.22 (broad, 48H), 1.27 (m, 432H), 0.88 (t,  $J$  = 6.7 Hz, 72H).

<sup>13</sup>C{<sup>1</sup>H}NMR of [(**1b**)<sub>6</sub>(H<sub>2</sub>O)<sub>8</sub>] (100 MHz, CDCl<sub>3</sub>, 25 °C, 65 mM):  $\delta$  = 151.34, 151.03, 125.51, 124.50, 103.47, 103.33, 33.97, 33.78, 32.63, 30.47, 30.40, 30.40, 30.40, 30.35, 30.09, 28.77, 23.38, 14.79 ppm.

<sup>1</sup>H NMR of (**2b**)<sub>6</sub> (400 MHz, CDCl<sub>3</sub>, 25 °C, 60 mM):  $\delta$  = 8.77 (s, 24H), 7.46 (s, 24H), 6.88 (s, 24H), 6.83 (s, 24H), 4.37 (t,  $J$  = 7.9 Hz, 24H), 2.21 (broad, 48H), 1.27 (m, 432H), 0.88 (t,  $J$  = 6.4 Hz, 72H).

<sup>13</sup>C{<sup>1</sup>H}NMR of (**2b**)<sub>6</sub> (100 MHz, CDCl<sub>3</sub>, 25 °C, 60 mM):  $\delta$  = 139.19, 138.05, 132.08, 126.08, 124.76, 114.48, 34.79, 33.86, 32.66, 30.60, 30.49, 30.49, 30.44, 30.44, 30.44, 30.13, 23.40, 14.81 ppm.

The stability of the capsules was studied by titrations of a 3 mM solution of the macrocycle in CDCl<sub>3</sub> or CHCl<sub>3</sub> with CD<sub>3</sub>OD. The samples were measured 20 min after the addition of methanol.

The role of water molecules was investigated by measuring the diffusion coefficients of samples containing different amounts of water. This was achieved by preparing different concentrations of the macrocycles (in the range of 3–60 mM) in different sources of chloroform such as water-saturated CDCl<sub>3</sub> (equilibrated with H<sub>2</sub>O three times 1:1 v/v), commercial CDCl<sub>3</sub> (as supplied from Aldrich, U.S.A., 99.8% D), and CDCl<sub>3</sub> from ampules (as supplied from Aldrich, U.S.A., 100% D). When necessary, to achieve a desired ratio of water/macrocycle, water was added to the CDCl<sub>3</sub> solutions.

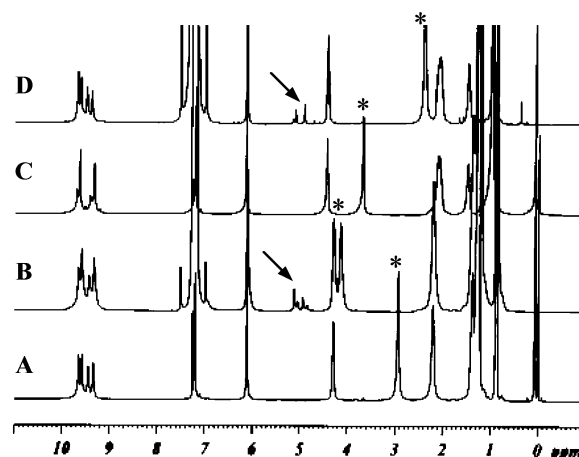
The self-recognition process was studied by measuring the diffusion coefficients of different mixtures of the macrocycles. Each mixture contained two different macrocycles in a ratio of about 1:1 in a solution of commercial CDCl<sub>3</sub>. The samples were measured almost immediately after preparation and several hours, days, and weeks later. The concentration of each macrocycle in the mixture was in the range of 10–15 mM.

The difference in guest affinity was studied by following the <sup>1</sup>H NMR spectra of the macrocycles in the presence of different guests. The amines were added to 10 mM CDCl<sub>3</sub> or 20 mM CHCl<sub>3</sub> solutions of the macrocycles, and the ratio was about 1:2 macrocycle/guest. The trialkylammonium salts were prepared in situ by adding about 40–60  $\mu$ L of DCl to a 0.4 mL solution of the macrocycle and the respective trialkylamine.

## Result and Discussion

**Self-Assembly in Solution. The Nature of the Formed Capsule.** Table 1 shows the diffusion coefficients of **1a**, **1b**, **2a**, and **2b** in chloroform solutions. The diffusion coefficients of all four molecules are relatively low, and after the addition of CD<sub>3</sub>OD, there is a significant increase in the diffusion coefficients in all four cases. These results indicate that these molecules form aggregates in the CDCl<sub>3</sub> solution, which disaggregate by the addition of methanol, a solvent which disrupts hydrogen bonds, thus resulting in an increase in the diffusion coefficients.

The diffusion coefficients of **1b** and **2b** are very similar and are somewhat lower than that of **1a** and **2a**, which is consistent



**Figure 1.** <sup>1</sup>H NMR spectra (400 MHz, 298 K) of (A) **1b** in CDCl<sub>3</sub>, (B) **1b** in CHCl<sub>3</sub>, (C) **1a** in CDCl<sub>3</sub>, and (D) **1a** in CHCl<sub>3</sub>. The arrows indicate the peaks of the encapsulated chloroform molecules. \* indicates signals of water.

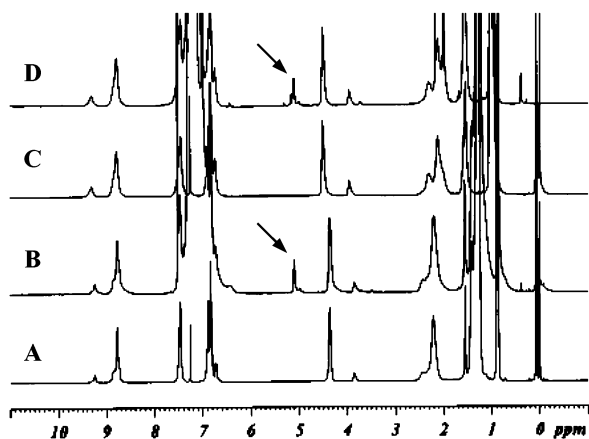
with the higher molecular weights of **1b** and **2b** (Table 1). These results indicate that **1a** and **2a** indeed form hexameric aggregates in the CDCl<sub>3</sub> solution as previously demonstrated for **1b**<sup>16a,19</sup> and **2b**.<sup>16c</sup> To further corroborate the formation of hexameric capsules, the molecular capsules were also prepared in CHCl<sub>3</sub>. Figure 1 shows the <sup>1</sup>H NMR spectra of **1b** (A and B) and **1a** (C and D) in CDCl<sub>3</sub> (A and C) and CHCl<sub>3</sub> (B and D). When **1a** and **1b** were dissolved in CHCl<sub>3</sub>, the same spectra were obtained with additional signals in the range of 4.8–5.1 ppm, which is about 2 ppm upfield from bulk chloroform. These new peaks had the same diffusion coefficients as that of the macrocycle (Table 1) and disappeared after the addition of CD<sub>3</sub>OD to the CHCl<sub>3</sub> solutions. Therefore, these new peaks were attributed to the encapsulated chloroform molecules, as previously determined for **1b**.<sup>16a</sup>

Figure 2 shows the <sup>1</sup>H NMR spectra of **2b** (A and B) and **2a** (C and D) in CDCl<sub>3</sub> (A and C) and in CHCl<sub>3</sub> (B and D). Here again, when **2a** and **2b** were dissolved in CHCl<sub>3</sub> the same spectra were obtained with an additional signal at 5.1 ppm, which was found to have the same diffusion coefficient as that of their respective macrocycle (Table 1). These new signals disappeared after the addition of CD<sub>3</sub>OD and were also attributed to the encapsulated chloroform molecules.

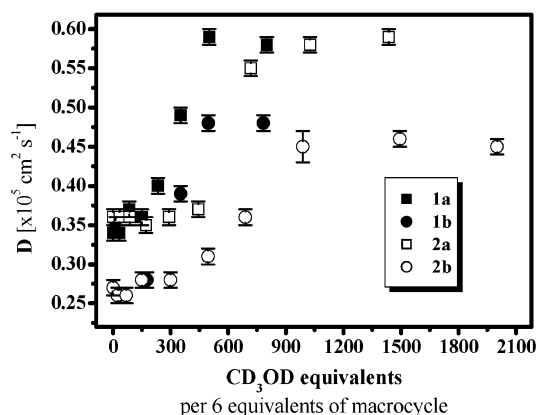
In addition, we found that the diffusion coefficients of the molecular capsules were the same, within experimental error, as those extracted for their respective complexes with guests, where the 6:1 stoichiometry could be deduced, unequivocally, from the integration of their <sup>1</sup>H NMR spectra.<sup>11b,16a</sup> Thus, if we conclude that the aggregates formed are indeed the hexamers found in the solid state, from the integration of the encapsulated

(19) Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 3432–3433.





**Figure 2.**  $^1\text{H}$  NMR spectra (400 MHz, 298 K) of (A) **2b** in  $\text{CDCl}_3$ , (B) **2b** in  $\text{CHCl}_3$ , (C) **2a** in  $\text{CDCl}_3$ , and (D) **2a** in  $\text{CHCl}_3$ . The arrows indicate the peaks of the encapsulated chloroform molecules.



**Figure 3.** Changes in the diffusion coefficients of **1a** (■), **1b** (●), **2a** (□), and **2b** (○) (in a 3 mM  $\text{CDCl}_3$  solution, 298 K) as a function of the number of equivalents of  $\text{CD}_3\text{OD}$  added to the  $\text{CDCl}_3$  solution.

chloroform peaks in the  $^1\text{H}$  NMR spectra obtained when the systems were prepared in  $\text{CHCl}_3$ , we conclude that about six chloroform molecules are encapsulated in the hexamers. These results indicate that **1a** and **2a** self-assemble spontaneously into hexameric capsules in chloroform solutions by encapsulating several chloroform molecules, as previously found for **1b** and **2b**.<sup>16a,c,19</sup>

**Relative Stability in Polar Media.** Atwood and co-workers claimed that **2a** appears to be stable even in polar solvents.<sup>12b</sup> We used diffusion NMR to study the relative stability of the molecular capsules of **1a**, **1b**, **2a**, and **2b** in chloroform solutions. To do so, we followed the changes in the diffusion coefficients of the macrocycles after the addition of different amounts of  $\text{CD}_3\text{OD}$ . Figure 3 shows the effect of these  $\text{CD}_3\text{OD}$  titrations on the diffusion coefficients of **1a**, **1b**, **2a**, and **2b** in the  $\text{CDCl}_3$  solutions. As a result of these titrations, an increase in the diffusion coefficients of all four macrocycles was observed. Methanol breaks the intermolecular hydrogen bonds, thus converting the hexameric capsules into their respective monomeric species. Figure 3 shows that different amounts of  $\text{CD}_3\text{OD}$  were required to disrupt the hexameric capsules in each case. The diffusion coefficient of **1a** increased from  $0.34 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  to  $0.59 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  upon addition of  $\sim 500$  equiv of  $\text{CD}_3\text{OD}$  (Figure 3), while the diffusion coefficient of **2a** increased from  $0.36 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  to  $0.55 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  only after the addition of about

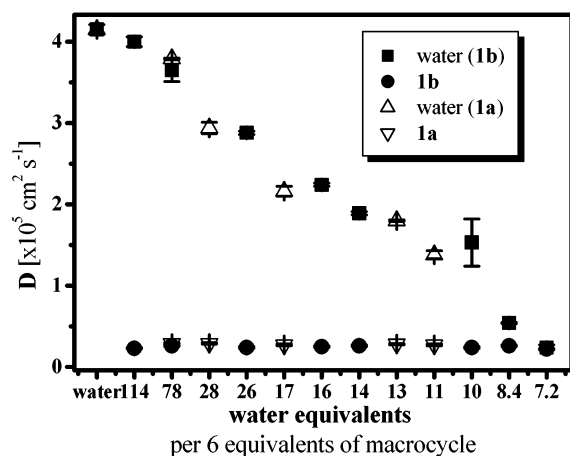
800 equiv of  $\text{CD}_3\text{OD}$ . For **1b**, the increase in the diffusion coefficient was from  $0.26 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  to  $0.48 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  and occurred after the addition of  $\sim 500$  equiv of  $\text{CD}_3\text{OD}$ , while for **2b**, the increase from  $0.27 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  to  $0.45 \pm 0.02 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  occurred only after adding 1000 equiv of  $\text{CD}_3\text{OD}$ .

According to these titrations, more methanol was needed to disrupt the hexamers of **2a** and **2b** than those of **1a** and **1b**. This suggests that the molecular capsules of the pyrogallol[4]-arenes are more stable than the capsules of the resorcin[4]arenes. It seems that the difference in stability is larger for the more lipophilic capsules (**1b** and **2b** vs **1a** and **2a**), which may indicate that the substituents on the methylene bridges influence the stability of the hexameric capsules formed in solution. We repeated these titrations in  $\text{CHCl}_3$  solutions to find the point of the titration at which the peaks of the encapsulated chloroform molecules disappear. In all four cases the peaks of the encapsulated chloroform disappeared before the diffusion coefficients of the different macrocycles reached their highest plateau values, i.e., before a complete disaggregation was achieved. This behavior was more pronounced in the cases of **1a** and **1b** than **2a** and **2b**. For the resorcin[4]arene capsules (i.e., **1a** and **1b**), most of the signals of the encapsulated chloroform molecules disappeared before there was any change in the diffusion coefficients of the hexamers, while for the pyrogallol[4]arene capsules (i.e., **2a** and **2b**), the disappearance of the encapsulated  $\text{CHCl}_3$  signal was observed only after a small increase in the diffusion coefficients of the hexamers. One possible explanation for the above observation is that the addition of methanol results in the loosening of the hydrogen bonds, which causes an increase in the exchange rate between the encapsulated and bulk chloroform. In addition, recently Rebek and co-workers, who studied the mechanism of guest exchange in such capsules, demonstrated that guest exchange in these systems probably does not require the complete disintegration of the hexamer.<sup>20</sup>

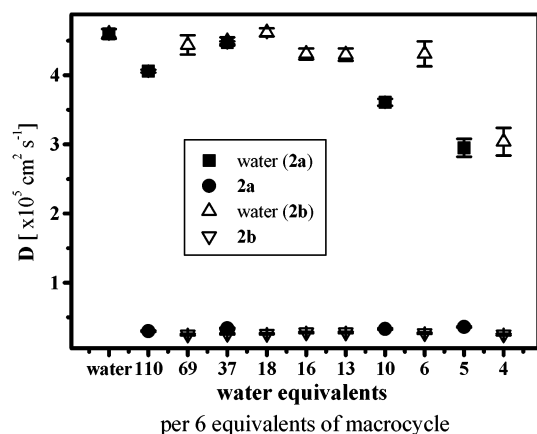
**The Role of Water Molecules.** It was found, in the solid state, that **1c** self-assembles into hexameric capsules with the aid of water molecules,<sup>11a</sup> while the hexameric capsule of **2a** does not.<sup>12</sup> We previously showed that the role of water molecules is different in the self-assembly of **1b** and **2b** in chloroform solutions.<sup>16b,c</sup> While **1b** self-assembles into a hexameric capsule of the  $[(\text{1b})_6(\text{H}_2\text{O})_8]$ -type, **2b** forms the hexamer of the  $[(\text{2b})_6]$ -type.<sup>16b,c</sup> We therefore wanted to investigate if the role of water molecules in the self-assembly of **1a** and **2a** is dictated by the lipophilicity of the macrocycles, i.e., the nature of R, or by the skeleton type, i.e., the number of the OH groups on the aromatic rings of the macrocycles.

We prepared  $\text{CDCl}_3$  solutions of **1a** and **2a** with different ratios of water/macrocycle. In all cases, only one peak of water was observed, indicating that if there are different water pools they are in fast exchange on the time scale of our NMR measurements. In the case of **1a**, we found that the **1a**/ $\text{H}_2\text{O}$  ratio affects both the chemical shift and line shape of the water signal. Since the water chemical shift and line shape were affected by other parameters such as pH and temperature, here again diffusion NMR was used to study the role of water molecules in the self-assembly of these molecules. Figures 4 and 5 show the changes in the diffusion coefficients of **1a**, **1b**

(20) Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2939–2943.



**Figure 4.** Diffusion coefficients of **1b** (●), **1a** (▽), and water in the solution of **1b** (■)<sup>16b</sup> and **1a** (△) as a function of the number of water equivalents per 6 equiv of the macrocycle.

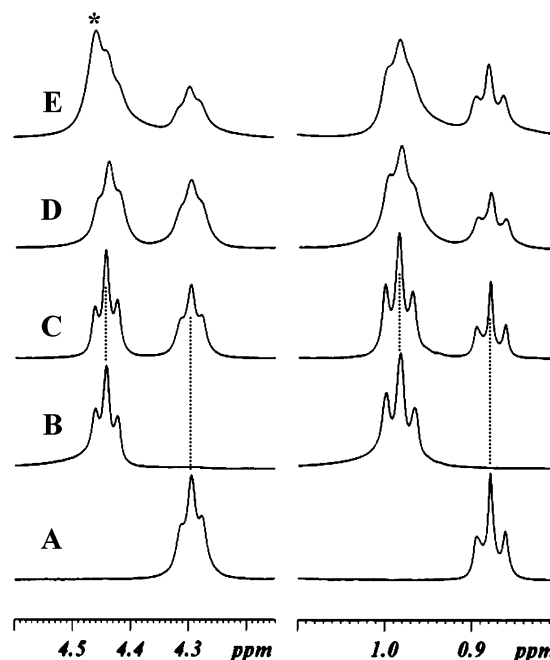


**Figure 5.** Diffusion coefficients of **2a** (●), **2b** (▽), and water in the solutions of **2a** (■) and **2b** (△)<sup>16c</sup> as a function of the number of water equivalents per 6 equiv of the macrocycle.

and of **2a** and **2b** and the water in their chloroform solutions. Figure 4 shows that the ratio of **1a**/H<sub>2</sub>O has a dramatic effect on the diffusion coefficient of the water signal, as previously found for **1b**.<sup>16b</sup> It was found that the diffusion coefficient of the water peak decreased as the number of water molecules per hexamer decreased. The changes in the diffusion coefficient of water in the presence of **1a** are very similar to that of water in the presence of **1b**. This seems to indicate that, like **1b**,<sup>16b</sup> **1a** self-assembles to a hexamer with eight water molecules, affording a capsule of the [(**1a**)<sub>6</sub>(H<sub>2</sub>O)<sub>8</sub>]-type.

For the **2a** system, only one peak of water was observed at all **2a**/H<sub>2</sub>O ratios and the chemical shift of the water peak was in the range of 1.5–1.6 ppm for all CDCl<sub>3</sub> solutions. The **2a**/H<sub>2</sub>O ratio had nearly no effect on the chemical shift of the water signal and only a marginal effect on the diffusion coefficients of the water peak in these CDCl<sub>3</sub> solutions. Here, only when the amount of water was extremely low, could some decrease in the diffusion coefficients of the water peak be observed, as previously found in the case of **2b**.<sup>16c</sup>

The diffusion data clearly show that water molecules do not participate in the self-assembly of the hexameric capsule of **2a** and **2b**. There is a slight decrease in the diffusion coefficient of the water peak when the ratio between **2a** and water is 6:5, which may be due to exchange with the hydroxyl groups of the macrocycle. Nevertheless, the diffusion coefficient of the water



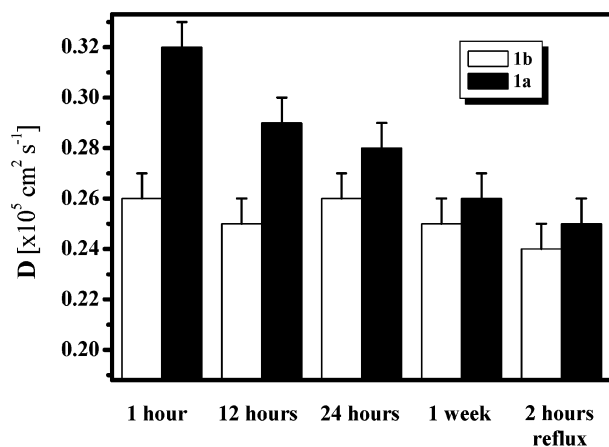
**Figure 6.** Sections of the <sup>1</sup>H NMR spectra of (A) **1b**, (B) **1a**, (C) a mixture of **1a** and **1b** in CDCl<sub>3</sub> solutions 1 h after preparation, (D) same as (C) one week later, and (E) a similar mixture that was heated to 65 °C for 2 h. The \* represents the peak of H<sub>2</sub>O in this CDCl<sub>3</sub> solution.

peak remained very similar to that of “free” water in CDCl<sub>3</sub>, indicating that the water molecules have hardly any interaction with the supramolecular structure of **2a** and **2b**. These results are in agreement with solid-state findings<sup>12</sup> and demonstrate that the role of water molecules is dictated by the number of OH groups on the aromatic ring rather than by the nature of the R groups.

**Self-Recognition in Self-Assembly.** Self-recognition in self-assembly processes was defined by Lehn and co-workers as “the recognition of like from unlike, of self-from nonself”.<sup>21a</sup> Self-recognition is a programmed supramolecular process of a spontaneous selection and preferential binding of like species in a mixture.<sup>21a</sup> The importance of self-recognition in the self-assembly of synthetic helicates was demonstrated by Lehn and co-workers.<sup>21</sup> This principle was further challenged by an extensive study of helicates with different binding sites.<sup>22a,b</sup> Other examples of self-recognition were found in the solid state.<sup>22c</sup>

After exploring the self-assembly of the four different macrocycles (**1a**, **1b**, **2a**, and **2b**) and examining the stability of the formed hexamers obtained in these processes, the self-assembly processes of mixtures of these molecules were studied. All six mixture combinations between the four macrocycles were studied with the aim of evaluating if the self-assembly of these hexameric capsules proceeds with self-recognition for macrocycles of the same type when only the R groups differ or across the different types of macrocycles, i.e., when R' is different (i.e., R' of H or OH). Figure 6 shows sections of the <sup>1</sup>H NMR spectra

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- (22) (a) Shaul, M.; Cohen, Y. *J. Org. Chem.* **1999**, *64*, 9358–9364. (b) Greenwald, M.; Wessely, D.; Katz, E.; Willner, I.; Cohen, Y. *J. Org. Chem.* **2000**, *65*, 1050–1058. (c) Malone, J. F.; Murray, C. M.; Nieuwenhuysen, M.; Stewart, G.; Docherty, R.; Lavery, A. J. *Chem. Mater.* **1997**, *9*, 334–338.

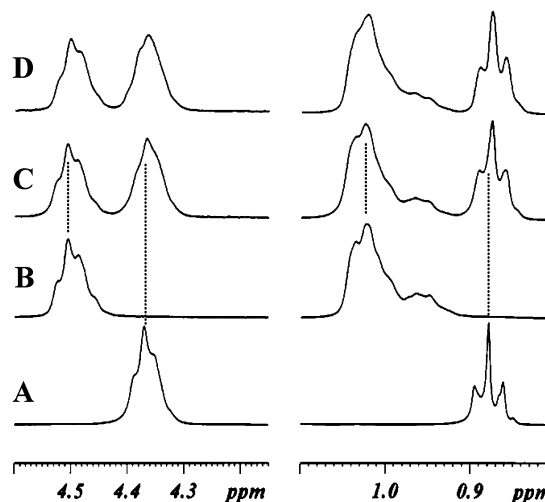


**Figure 7.** Diffusion coefficients of **1a** (■) and **1b** (□) as a function of time after preparation of the mixture and after 2 h of reflux.

of **1b** (Figure 6A), **1a** (Figure 6B), and a mixture of **1a** and **1b** in  $\text{CDCl}_3$  solutions nearly immediately and one week after the preparation of the sample (Figure 6C,D, respectively). Figure 6E shows these sections of the  $^1\text{H}$  NMR spectrum of a mixture of **1a** and **1b** after 2 h of reflux.

Figure 6 clearly shows that the spectra of the mixtures are mere superpositions of the spectra of **1a** and **1b** regardless of the temperature and the elapsed time since the mixing of the compounds. In all cases, no other signals are observed. When we measured the diffusion coefficients of the signals of the mixture shown in Figure 6C, two different diffusion coefficients were extracted. The diffusion coefficient of the peaks of the hexamer of **1a** in the mixture was  $0.32 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  and that of the hexamer of **1b** was  $0.26 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ . In general, the ratio between the diffusion coefficients of two species should be inversely proportional to the cube or the square root of the ratio of their molecular weights. The ratio between the diffusion coefficients of the peaks of **1a** and **1b** in the mixture is 1.2, which is in good agreement with this prediction. On the basis of these findings one might conclude that, indeed, the self-assembly of **1a** and **1b** proceeds with complete self-recognition, implying the formation of only homo-hexamers. However, a close look at the effect of time and temperature on the diffusion coefficients of the hexamers mixtures, shown in Figure 7, demonstrates that this is not the case.

Figure 7 shows that the diffusion coefficients of the two hexamers differed immediately after the preparation of the mixture. However, as time passed, a process of equalization in the diffusion coefficients was observed. After 24 h there was only a small difference in the diffusion coefficients of the two systems. After one week, the difference was within the experimental error and was statistically insignificant. Therefore, we hypothesized that, in the beginning, we have two homo-hexamers that mix slowly with time. Indeed, when the mixture was refluxed for 2 h, the same diffusion coefficient was found for the two peaks representing **1a** and **1b**. Upon warming, the mixing of the capsules is faster, as shown in Figure 7. It should be noted that this conclusion could not be reached from the  $^1\text{H}$  NMR spectra since only marginal changes were observed in the spectra over time or after the 2 h of reflux (Figure 6). Even when the diffusion coefficients of **1a** and **1b** were the same, within experimental error, the  $^1\text{H}$  NMR spectra showed two



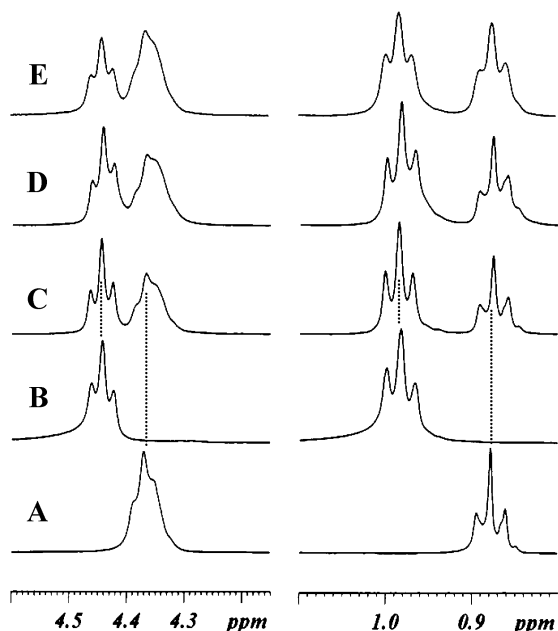
**Figure 8.** Sections of the  $^1\text{H}$  NMR spectra of (A) **2b**, (B) **2a**, (C) a mixture of **2a** and **2b** in chloroform solutions 1 h after preparation, and (D) same as (C) one week later.

distinct sets of peaks for **1a** and **1b** with no indication for the formation of the heterohexamers. Figure 8 shows sections of the  $^1\text{H}$  NMR spectra of **2a**, **2b**, and a mixture of **2a** and **2b** both 1 h and 1 week after the preparation of the mixture.

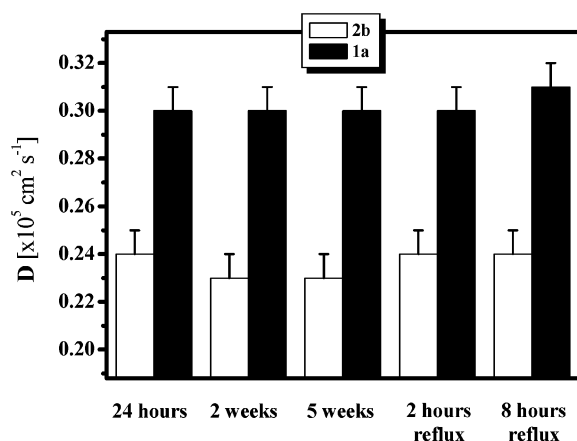
Here again the  $^1\text{H}$  NMR spectrum of the mixture shows only signals of **2a** and **2b**, and no other signals could be detected. The diffusion coefficients of the peaks of **2a** and **2b** in the mixture, almost immediately after preparation, were  $0.34 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  and  $0.28 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ , respectively. The ratio between the diffusion coefficients of the peaks of **2a** and **2b** in the mixture is 1.2, which is in good agreement with the value extracted based on their relative molecular weights. However, here again, the diffusion coefficients equalized as the time from the preparation of the mixture elapsed. These results indicate that, with time, an equilibrium is achieved in which the homo-hexamers are replaced by heterohexamers consisting of **2a** and **2b**, similar to the case of **1a** and **1b**.

The above two cases dealt with mixtures of the same type of macrocycles (two resorcin[4]arenes or two pyrogallol[4]arenes) that differ in their substituents on the bridges ( $\text{R} = \text{C}_{11}\text{H}_{23}$  or isobutyl). Next we examined whether the self-assembly of two different macrocycle types proceed with self-recognition. Figure 9 shows sections of the  $^1\text{H}$  NMR spectra of **2b** (Figure 9A), **1a** (Figure 9B), and a mixture of **2b** and **1a** (Figure 9C,D) in  $\text{CDCl}_3$  solutions 24 h and 5 weeks after the preparation; Figure 9E shows the same sections of the  $^1\text{H}$  NMR spectrum of a mixture of **2b** and **1a** after 8 h of reflux.

It was found that the  $^1\text{H}$  NMR spectrum of the mixture is a superposition of the spectra of the homo-hexamers, as was found for the two mixtures above (Figures 6 and 8). Even 5 weeks of mixing time or 8 h of reflux did not meaningfully change the appearance of the  $^1\text{H}$  NMR spectrum of the mixture. However, the results from the diffusion measurements were quite different. Two diffusion coefficients were extracted for the peaks of **1a** and **2b** 24 h after the preparation of the sample. The values were found to be  $0.30 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  and  $0.24 \pm 0.01 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$  for the peaks of **1a** and **2b**, respectively. These values are in line with the molecular weight of the homo-hexamers. However, to our surprise, although the same behavior was observed in the  $^1\text{H}$  NMR spectra, here the differences in the



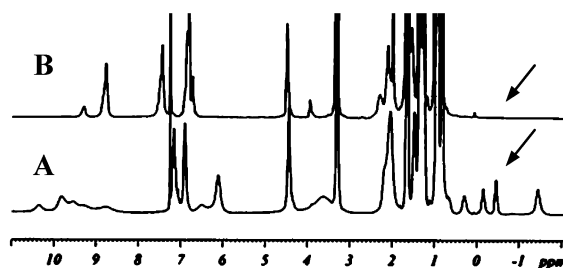
**Figure 9.** Sections of the <sup>1</sup>H NMR spectra of (A) **2b**, (B) **1a**, (C) a mixture of **2b** and **1a** in CDCl<sub>3</sub> solutions 24 h after preparation, (D) same as (C) but five weeks later, and (E) after 8 h at 65 °C.



**Figure 10.** Diffusion coefficients of **1a** (■) and **2b** (□) as a function of the time after preparation of the mixture and after 2 and 8 h of reflux.

diffusion coefficients remained constant even after 5 weeks of mixing. Additionally, after reflux of the mixture for more than 8 h, two distinct diffusion coefficients were found, as shown in Figure 10, although in the case of the mixture of **1a** and **1b**, less than 2 h of reflux were required to obtain a single diffusion coefficient for all peaks in the <sup>1</sup>H NMR spectrum.

The results obtained for **1a** and **2b** are in contrast to results obtained for the mixtures of **1a** and **1b** or **2a** and **2b**, where heterohexamers are formed. In the mixtures of **1a** and **2b** or **1b** and **2a** (data not shown) no heterohexamers are formed. Therefore, one can conclude that, across the macrocycle types, the self-assembly proceeds with self-recognition, while within the macrocycle type heterohexamers can be formed with time. We could not reach definite conclusions regarding the mixtures of **1a** and **2a** or **1b** and **2b** since, as previously demonstrated, the <sup>1</sup>H NMR spectra are not indicative enough regarding the formation of hetero- or homohexamers, and in contrast to the mixtures mentioned above, diffusion NMR cannot be used to investigate the process in these cases. The compounds in these



**Figure 11.** <sup>1</sup>H NMR spectra of **1a** (A) and **2a** (B) in CDCl<sub>3</sub> solutions in the presence of THABr. The arrows indicate the chemical shift region anticipated for encapsulated ammonium salts.

mixtures happen to have very similar molecular weights and, hence, very similar diffusion coefficients so that the homo- and heterohexamers cannot be distinguished on the basis of their diffusion coefficients.

It seems that different types of macrocycles, i.e., the resorcin[4]arenes and the pyrogallol[4]arenes, are sufficiently “self-instructed” to avoid the formation of heterocapsules, while the two resorcin[4]arenes (**1a** and **1b**) and pyrogallol[4]arenes (**2a** and **2b**) form heterocapsules. Interestingly, the results clearly show that chemical shifts could not be used to determine in which case the self-assembly proceeds with self-recognition and in which it does not, while diffusion NMR provides unequivocal information regarding this issue.

**Guest Affinity.** One of the most intriguing characteristics of molecular capsules is their ability to encapsulate guest molecules. This enables the stabilization of the reactive intermediates<sup>8</sup> and the catalysis of reactions.<sup>9</sup> This is even more important for molecular capsules having large cavities, which can, in principle, accommodate more than one guest molecule. Therefore, understanding the factors that influence the affinity of guests toward the cavity of molecular capsules is important. Steric factors play a crucial role,<sup>23</sup> and guest molecules that are too large will have a much lower affinity toward the capsule’s cavity. Electronic factors may also have some influence on the guest affinity.<sup>15b,c</sup> It was shown that charged guests, such as tetraalkylammonium salts, a tropylium cation, or a cobaltocenium cation, have high affinities toward the cavity of the dimers of tetraareacalix[4]arenes, probably because of  $\pi$ –cation interactions.<sup>15b,c,24</sup> Kaifer recently reported that **1b** encapsulates a cobaltocenium cation but not cobaltocene.<sup>25</sup> Therefore, it seems that there should be a preference for charged guests in these systems. However, we found that, while the hexamer of **1b** can accommodate both neutral tertiary alkylamines and charged quaternary alkylammoniums, **2b** encapsulates only the tertiary alkylamine series.<sup>26</sup> To examine whether this is a general characteristic of these types of molecular capsules, we also studied the guest affinity of **1a** and **2a**. Here again, all our attempts to probe encapsulation of tetraalkylammonium salts in the hexameric capsule of **2a** failed as shown in Figure 11. After the addition of tetrahexylammonium bromide (THABr) to a CDCl<sub>3</sub> solution of **1a** the typical high field chemical shifts of the encapsulated alkylammonium salts appeared (Figure 11A), which did not happen in the case of **2a** (Figure 11B).

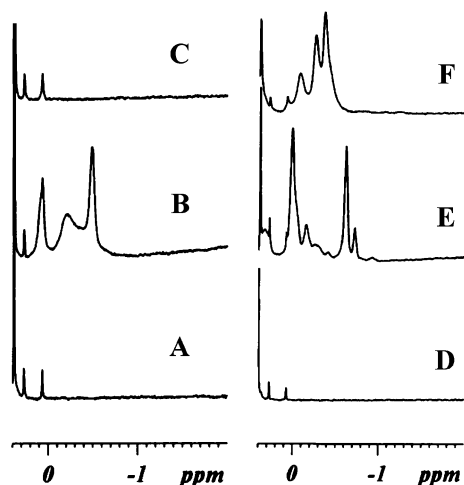
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**Figure 12.** Sections of the  $^1\text{H}$  NMR spectra (400 MHz, 298 K) of the hexameric capsules of **2a** (A–C) and **1a** (D–F) in  $\text{CHCl}_3$  (A) and (D), after the addition of trihexylamine (B) and (E) and after the addition of DCl (C) and (F).

When alkylammonium salts were added to the  $\text{CHCl}_3$  solutions of **2a**, the signal of the encapsulated chloroform prevailed and there were no indications of the formation of hexameric capsules encapsulating the alkylammonium salts. In some cases, alkylammonium salts with anions different from  $\text{Br}^-$  (i.e.,  $\text{Cl}^-$ ,  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ ) were used and the same qualitative results were obtained. Therefore, encapsulation of noncharged molecules, such as alkylamines, into the hexamer of **2a** was attempted. Figure 12 shows sections of the  $^1\text{H}$  NMR of **2a** and **1a** in  $\text{CHCl}_3$  before (Figure 12A,D) and after (Figure 12B,E) the addition of trihexylamine. Parts C and F of Figure 12 show these sections of the  $^1\text{H}$  NMR spectra after addition of DCl to the solutions shown in Figure 12B,E, respectively. DCl transforms the neutral amines into their respective ammonium salts without significantly affecting the size of the guests.

These spectra clearly demonstrate that the addition of trihexylamine resulted in the appearance of new signals at higher field in both the solutions of **1a** (Figure 12E) and **2a** (Figure 12B). The addition of the amine resulted in the disappearance of the signals of the encapsulated chloroform molecules from the capsules of **1a** and **2a**. When DCl was added to this solution, the ammonium salt was formed, which led to the ejection of the guest from the cavity of **2a** (Figure 12C) and the reencapsulation of the chloroform molecules. However, both the amine (Figure 12E) and the ammonium salt (Figure 12F) are encapsulated in the hexameric capsule of **1a**. The same results were obtained for tributylamine and trioctylamine and their respective ammonium salts, as previously observed for the hexameric capsules of **1b** and **2b**.<sup>26</sup> All these findings indicate that, while **1a** and **1b** accommodate both the amines and the respective ammonium salts, the hexameric capsules of **2a** and **2b** can encapsulate only the neutral amines. In fact, the protonation of the tertiary amines resulted in the ejection of the guests from the capsules of **2a** and **2b**. These experiments demonstrate that

the difference in guest affinities between the hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes is indeed a general phenomenon, unaffected by the nature of the alkyl chains on the methylene bridges or the lipophilicity of the macrocycles. It is rather the different interactions between the two types of macrocycles and the charged guests that seem to determine the affinity. On the basis of electron density arguments, one should expect the capsules of **2a** and **2b** to have a higher affinity to charged systems as compared to the capsules of **1a** and **1b** in contrast with the experimental results. Therefore, it seems that the differences in the guests affinities of these two types of hexameric capsules are mainly connected to their different structures, hydrogen bond capability, and the different role that the water molecules play in these capsules.

## Conclusions

In the present study, diffusion NMR was used to follow the self-assembly of resorcin[4]arenes **1a** and **1b** and pyrogallol[4]arenes **2a** and **2b** in  $\text{CDCl}_3$  solutions. From this diffusion NMR data, we could conclude that **1a**, **1b**, **2a**, and **2b** form hexameric capsules in chloroform solutions of nearly equal stability although it seems that the latter are more stable than the former to addition of a polar solvent. We also found that the role of water and the guest affinity of the hexameric capsules of **1a** and **1b** are the same and different from that of the capsules of **2a** and **2b**. Water molecules were found to be part of the hexameric capsule in the case of resorcin[4]arenes **1a** and **1b** but not in the capsules of **2a** or **2b**. Despite the similar structure of the resorcin[4]arenes and pyrogallol[4]arenes and the fact that they all form hexameric capsules in chloroform, **2a** and **2b** were found to encapsulate only the neutral tertiary alkylamines while **1a** and **1b** accommodate both the amines and the respective ammonium salts. For **2a** and **2b**, the protonation of the tertiary amines resulted in the ejection of the guests from the capsules. All these observations point toward the importance of the number of the OH groups on the aromatic moieties of these systems in determining the structure and guest affinity of these capsules. It seems that the nature of R (i.e., R = isobutyl or  $\text{C}_{11}\text{H}_{23}$ ), i.e., the lipophilicity of these compounds does not have a dramatic effect on the self-assembly of these capsules. In addition, it was found that the self-assembly process across the macrocycle type, i.e., when resorcin[4]arenes and pyrogallol[4]arenes are mixed, proceeds with self-recognition. Only homohexameric capsules of the same macrocycle type are formed from mixtures of different macrocycle types. However, the two resorcin[4]arenes (**1a** and **1b**) or two pyrogallol[4]arenes (**2a** and **2b**) can form heterohexameric capsules over time or after heating of the solutions. This was unequivocally demonstrated using diffusion NMR but could not be deduced from chemical shift arguments. This study clearly demonstrates the additional insights obtainable by diffusion NMR in such systems.

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