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Hydrogen-Bonded Hexameric Capsules of Resorcin[4]arene, Pyrogallol[4]arene and Octahydroxypyridine[4]arene are Abundant Structures in Organic Solvents: A View from Diffusion NMR

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Hydrogen-bond molecular capsules have attracted much interest in the last decade. In the present paper, we wish to describe new insights obtained from diffusion NMR when studying the self-assembly of resorcin[4]arenes (2), pyrogallol[4]arenes (3) and octahydroxypyridine[4]-arenes (4) in solution. These diffusion NMR studies demonstrate that compounds 2 and 3 self-assemble spontaneously into hexameric capsules in organic solvents. For compound 4, both hexameric capsules and dimeric aggregates were identified. Diffusion NMR was found to be very useful in evaluating the relative stability of these capsules as well as in determining the role played by water molecules in the self-assembly of such systems. Moreover, diffusion NMR enabled us to establish whether the self-assembly of these capsules proceeds with self-sorting. We could demonstrate that the hexamers of 3 are more stable than the hexameric capsules of 2 and that the formation of such hexamers proceeds with self-sorting and no hetero-hexamers are formed when macrocycles of different classes are mixed. The hexameric capsules of 2 were found to self-assemble with eight water molecules, whereas water molecules are not required for the formation of the hexameric capsules of 3. Diffusion NMR helped in demonstrating that many of the previously evoked 1:1 and 1:2 host–guest complexes of 2 are in fact hexamers encapsulating a multiplicity of guests. This supports the notion that hexameric capsules of these systems are much more abundant species in organic solvents than previously thought. These studies also demonstrate that diffusion NMR is an extremely useful tool for studying and characterising supramolecular systems and molecular capsules in solution.

Keywords: Supramolecular chemistry; Diffusion NMR; Hydrogen bond; Resorcin[4]arene; Pyrogallol[4]arene; Hexameric capsules; Octahydroxypyridine[4]arene; Container molecules

INTRODUCTION

Molecular capsules that may operate as drug delivery systems and as nanoreactors have attracted much attention in the last decade [1–3]. Previous studies have described the preparation of non-covalent molecular capsules based on different non-covalent interactions [1–7]. Here, we wish to concentrate on the structure and characteristics of hydrogen-bonded capsules based on calix[4]arene derivatives such as resorcin[4]arenes (**2**), pyrogallol[4]arenes (**3**) and pyridine[4]arenes (**4**). In the present paper, we will briefly review some of the insights gained from diffusion NMR on the molecular capsules of these systems.

From Dimeric to Hexameric Capsules

Rebek and then Böhmer were the first to realise that the peculiar spectra of tetraureacalix[4]arenes (**1**) in non-polar solvents arose from the formation of the dimeric capsules of these systems [8–10]. During the last decade, dimeric capsules of other related systems were prepared and were shown to encapsulate solvent molecules and other small guests [11–13]. These dimeric capsules are characterised by relatively small cavities [8–13].

The structure of the hexameric capsule of *C*-methyl resorcin[4]arene (**2c**) reported by Atwood was first regarded as a unique exotic structure [14]. Thereafter, the Mattay group provided some

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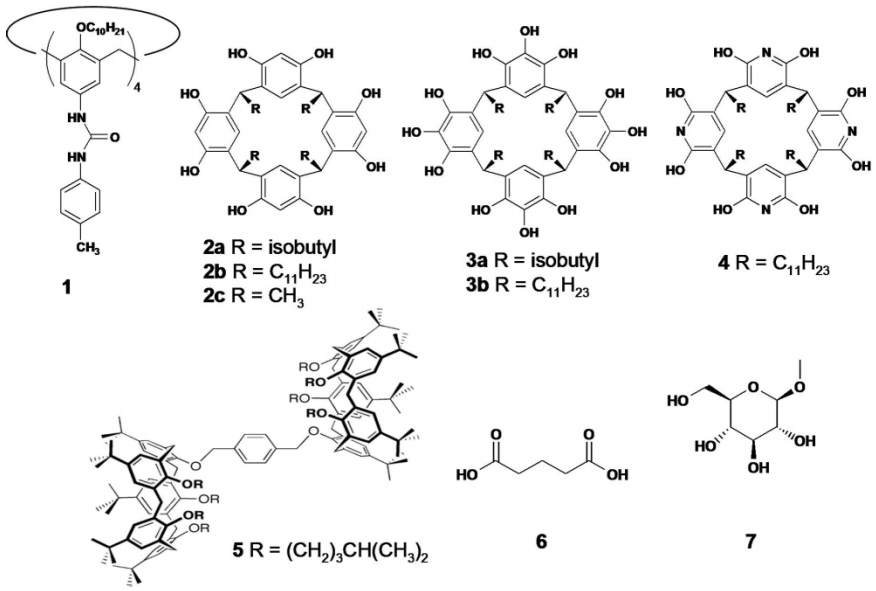

SCHEME 1 The structures of tetraureacalix[4]arenes (**1**), resorcin[4]arenes (**2**), pyrogallol[4]arenes (**3**), octahydroxypyridine[4]arenes (**4**), biscalix[5]arene (**5**), glutaric acid (**6**) and methyl β-D-glucopyranoside (**7**).

evidence concerning the formation of hexameric capsule of *C*-isobutyl pyrogallol-[4]arene (**3a**) in the solid state [15]. These capsules were found to have much larger cavities than the tetraurea calix[4]arene dimers [14–16]. In 2001, Shivanyuk and Rebek demonstrated that with the appropriate guests, such hexameric capsules of *C*-undecyl resorcin[4]arene (**2b**) can also be observed in organic solvents [17]. As will be demonstrated next, diffusion NMR has contributed considerably to the identification and characterisation of such hexameric capsules in solutions.

Diffusion NMR: A Tool for Studying Supramolecular Systems in Solution

Translational diffusion, which is the random walk performed by ions or molecules, can be measured relatively easily and accurately using pulsed-field gradient experiments [18–20]. The pulsed gradients spin echo (PGSE) [18] and the stimulated echo (STE) diffusion [19] pulse sequences are shown in Fig. 1(a) and (b), respectively. These sequences can be performed easily using conventional NMR spectrometers with the aid of the conventional gradient systems available on such NMR spectrometers. More than a decade ago, the LED [21] and bipolar LED (BPLED; [22]) sequences (Fig. 1(c) and (d)) were introduced by Johnson, who suggested the use of diffusion ordered spectroscopy (DOSY; [23]). DOSY provides 2D maps, in which one axis represents the chemical shift while the other represents the diffusion coefficient [23].

The diffusion coefficient in such experiments can be calculated using equation (1), [18]

$$\ln\left(\frac{I_{(2\tau,G}}{I_{(2\tau,0)}}\right) = -\gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3}\right) D = -bD, \quad (1)$$

where $I_{(2\tau,0)}$ and $I_{(2\tau,G}$ are the echo intensities at 2τ in the absence and the presence of gradient pulses, respectively, G is the pulsed gradient strength, Δ and δ are the time separation between the pulsed-gradients and their duration, respectively (Fig. 1), and D is the diffusion coefficient. The term $(\Delta - \delta/3)$ is generally referred to as the *diffusion time*.

The product $\gamma^2 G^2 \delta^2 (\Delta - \delta/3)$ is often abbreviated as the *b*-value, and represents the *diffusion weighting*. Thus, for an isotropic solution, a plot of $\ln(I_{(2\tau,G)}/I_{(2\tau,0)})$ vs. b should give a straight line, the slope of which is equal to D. In principle, any of the parameters, δ, Δ and G, can be varied to affect signal attenuation and thus providing a mean for measuring D. However, technical factors and the relaxation characteristics of the sample may limit our choice.

Since the diffusion coefficient of a given species is related to its effective molecular weight, it is clear that such a parameter may be useful in mapping intermolecular interactions. Indeed, more than a decade ago we decided to use diffusion NMR as an additional analytical method to probe intermolecular interactions in supramolecular systems in solution [24–32]. We have demonstrated that one can use diffusion coefficients to calculate association constants [24], map water hydration and complexation [28], and evaluate the intermolecular interactions in different supramolecular systems [24–32]. Diffusion was used, *inter alia*, to study the aggregation mode of charged molecules [26], to map the intermolecular interactions in macrocycle/cyclodextrin complexes [27] and other complexes of cyclodextrins [29], evaluate the integrity of single-, double- and tetra-rosettes [30], probe the formation of pseudorotaxanes [31] etc. Diffusion NMR was found to be extremely important in mapping intermolecular

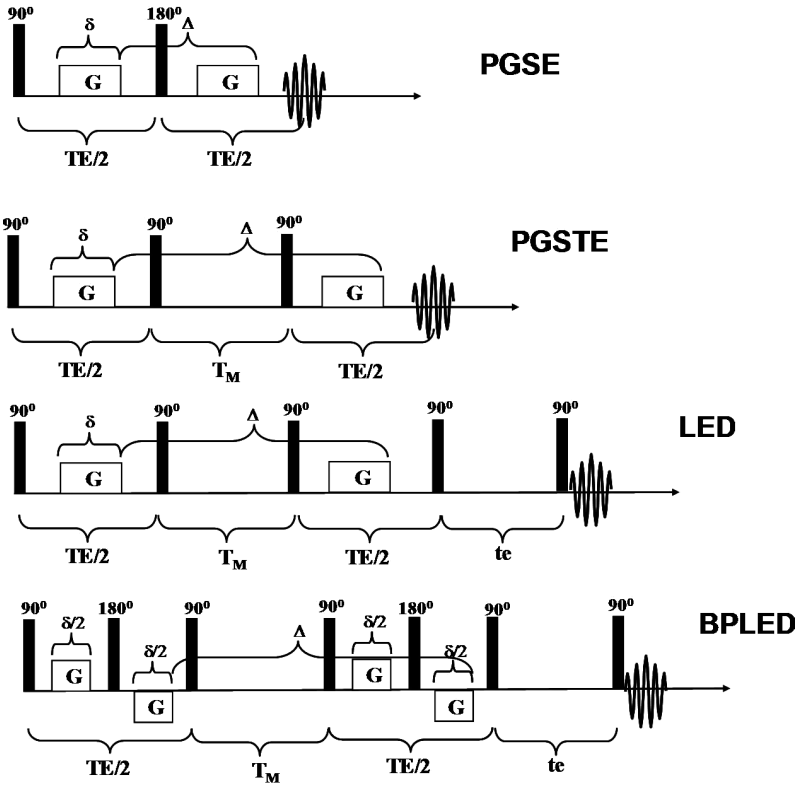

FIGURE 1 The (a) PGSE, (b) the STE diffusion, (c) the LED and (d) BPLED pulse sequences.

interactions in systems where the changes in chemical shifts upon complexation are marginal and in systems where proton transfer which may affect the chemical shifts dramatically, occurs. In the latter systems, when relaying on chemical shift differences, acid–base equilibriums may be confused with complexation processes [24]. Recently the application of diffusion NMR to the study of supramolecular and combinatorial chemistry was reviewed [32].

In 1999, we demonstrated the utility of diffusion NMR to probe the formation of hydrogen-bond molecular capsules of tetraurea calix[4]arenes such as compound **1** [33–35]. These dimeric capsules, which have a relatively small cavity, are generally constructed from three molecules (two hosts and one guest). We were interested in using diffusion NMR to characterise more complex systems that are constructed from more building units. For this purpose, the hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes seemed to be the system of choice.

SPONTANEOUS FORMATION OF HEXAMERIC CAPSULES

Our first objective was to evaluate the role of water molecules in the complex of **2b** with tetrahexylammonium bromide (THABr), first reported by Shivanyuk and Rebek [17]. However, in preliminary diffusion NMR measurements we found that, under the same experimental conditions, the diffusion coefficient of the hexameric capsule of **2b** with THABr is the same as the diffusion coefficient of **2b** in the $CDCl_3$ solutions. This led us to suspect that **2b** self-assembles spontaneously into hexameric aggregates in chloroform [36]. As we will demonstrate, by combining diffusion NMR and routine NMR spectroscopy it was relatively straightforward to provide convincing evidence for the formation of hexameric aggregates of systems such as **2**, **3** and **4** in different solvents. These hexameric aggregates were later shown to be hexameric capsules [36–40].

Figure 2 shows the signal decay of a representative peak of several molecular species in $CDCl_3$ as a function of the gradient strength (G) and demonstrates how simple it is to identify new hexameric aggregates, once one such a system has been identified. After establishing that **2b** forms hexameric aggregates one can easily identify other systems that form hexamers by just inspecting the signal decay as a function of the gradient strength or by calculating the diffusion coefficient of each species from the signal decay.

Figure 3 shows the signal decay as a function of the diffusion weighting (the b-values in equation 1) for the representative peaks shown in Fig. 2. Fig.s 2 and 3 clearly demonstrate that the signal decays of **2b**, **3b** and one of the peaks of **4** are very similar and are all slower than the signal decay of **5** and the other peak

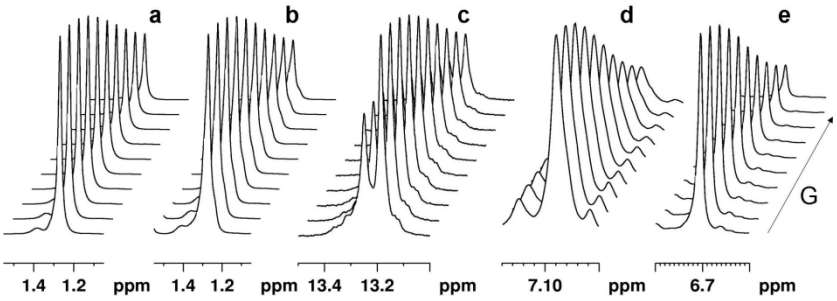

FIGURE 2 The stack plots of the signal decay as a function of the gradient strength (*G*) of a representative peak of the hexamers of (a) **2b**, (b) **3b**, (c) **4**, (d) the dimer of **4** and (e) **5** (3 mM $CDCl_3$, 298 K).

TABLE I Diffusion coefficients of **2b**, **3b** and **4** in chloroform at 298 K.

	Diffusion coefficients ($\times 10^5\,cm^2\,s^{-1}$)			
System (M_w)[a]	**2b** (1104 g mol^{-1})	**3b** (1168 g mol^{-1})	**4** (1108 g mol^{-1})	
20–25 mM in $CDCl_3$	0.24 ± 0.01	0.25 ± 0.01	0.24 ± 0.01	0.37 ± 0.01[b]
20 mM in $CHCl_3$	0.24 ± 0.01	0.24 ± 0.01	0.25 ± 0.01	0.36 ± 0.01[b]
	0.25 ± 0.01[c]	0.25 ± 0.01[c]	0.24 ± 0.01[c]	

[a] Molecular weights of the monomers; [b] The diffusion coefficient of the dimer of **4**; [c] The diffusion coefficient of the encapsulated chloroform molecules.

of **4**. Compound **5** [41] was used as an internal reference for species whose molecular weight was similar to that expected for the dimers of compounds **2b**, **3b** and **4**. The extracted diffusion coefficients are tabulated in Table I. Interestingly, **2b**, **3b** and one of the peaks of **4** were found to have the same diffusion coefficients as the hexameric capsule of **2b** with THABr, namely, $0.25 \pm 0.01 \times 10^{-5}$ $cm^2\,s^{-1}$ in chloroform solution (20–30 mM, 298 K).

These data clearly show that **2b** and **3b** form hexameric aggregates [36–39], whereas **4** forms both hexameric and dimeric aggregates [40]. Note that octahydroxypyridine[4]arene (**4**), which was first synthesised by the Mattay group [42], was recently claimed to form monomers and dimers [43]. To probe the capsular nature of these aggregates, we recorded the NMR spectra of these systems in $CHCl_3$ solutions, as shown in Fig. 4. In all these spectra we found new additional peaks that were found to have the same diffusion coefficients as the entire capsule and were, therefore, assigned to the encapsulated solvent molecules (Table I). The fact that there is a slow exchange on the NMR timescale when the guests are solvent molecules, which do not have any specific binding sites, suggests that the hexameric aggregates are, indeed, hexameric capsules in solution [2,6,36–40]. Interestingly, the results in solution are consistent with the results in the solid state for resorcin[4]arenes and pyrogallol[4]arenes [14–16].

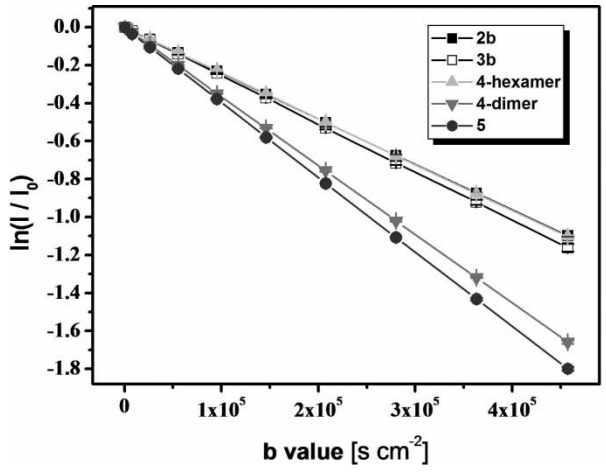

FIGURE 3 The signal decay as a function of the diffusion weighting (the *b*-value in Equation 1) of the representative peaks of the hexamers of **2b**, **3b**, **4**, the dimer of **4** and **5** depicted in Figure 2.

It was also found that such resorcin[4]arenes and the pyrogallol[4]arenes form hexameric capsules in different organic solvents, such as chloroform, benzene and methylene chloride [36–39]. A hexamer of **2b** encapsulates about eight benzene molecules, 5–6 chloroform molecules or 11 molecules of methylene chloride. Furthermore, we found that **3b** can accommodate the same number of chloroform and methylene chloride molecules but only five to six benzene molecules. For **3b**, we found that co-encapsulation of chloroform and benzene is favoured over encapsulation of a single type of solvent molecules [44].

In the case of **3b**, we found that the peak of the encapsulated chloroform appears as a septet. We could demonstrate that this signal consist of seven singlets [44]. Interestingly, we found that the chemical shifts of the encapsulated chloroform

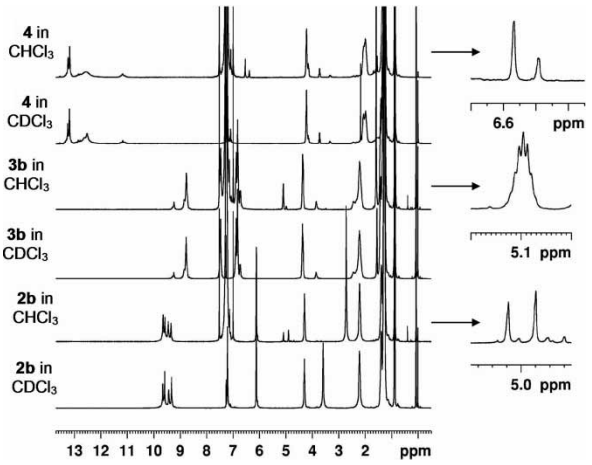

FIGURE 4 The ^{1}H NMR spectra of **2b**, **3b** and **4** in $CHCl_3$ and $CDCl_3$ solutions. The figure also shows expansions of the peaks of the encapsulated solvent molecules.

molecules are very similar in the hexamers of systems **2b** and **3b** but very different from that of the encapsulated chloroform in **4** [36–40].

RELATIVE STABILITY OF HEXAMERIC CAPSULES

To get some insight into the relative stability of the formed hexameric capsules in chloroform solutions, we titrated these solutions with methanol and observed the changes in the diffusion coefficients upon addition of methanol, as shown in Fig. 5.

This Fig. clearly demonstrates that the addition of methanol disaggregates the hexameric capsules of **2b** and **3b**. These data show that much less methanol is required to disaggregate the hexameric capsule of **2b** as compared with the hexameric capsules of **3b**. The addition of 250 equivalents of methanol suffices to disaggregate the hexamer of **2b,** but nearly 1000 equivalents of methanol are needed to disaggregate the hexamers of **3b**. Note that when we performed such titrations for **2b** and **3b** in $CHCl_3$ solutions we found that the peaks of the encapsulated chloroform disappear before disaggregation occurs.

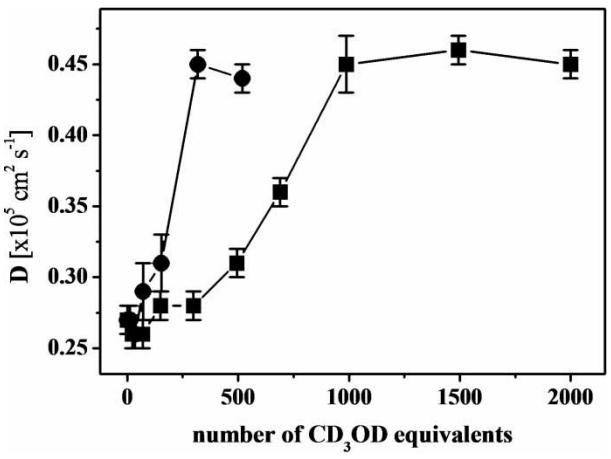

FIGURE 5 The effect of methanol titration on the diffusion coefficients of **2b** (●) and **3b** (■) (3 mM, $CDCl_3$, 298 K).

THE ROLE OF WATER MOLECULES IN THE SELF-ASSEMBLY OF HEXAMERIC CAPSULES

To evaluate the role of water, we followed the diffusion coefficients of the water molecules and the macrocycle in chloroform solutions where we changed the macrocycle:water ratio as shown in Fig. 6. In principle, water molecules can reside in three different pools: encapsulated, as part of the supramolecular structure and in the bulk of the chloroform solution. In all the chloroform solutions of **2b** and **3b**, only one water peak was observed for all water populations [37, 39, 45]. The observation of a single water peak in the chloroform solutions of **2b** and **3b** implies that the different water pools are in a fast exchange on the NMR timescale. Consequently, the measured diffusion coefficients should be a weighted average of the diffusion coefficients of water in the different pools.

The data presented in Fig. 6 shows that the macrocycle:water ratio has no effect on the diffusion coefficients of the macrocycles **2b** and **3b**. On the contrary, this ratio has a dramatic effect on the diffusion coefficient of the water molecules in the case of **2b** but not in the case of **3b**. Interestingly, in the case of **2b**, we found that when there were more than eight water molecules per six molecules of **2b**, the diffusion coefficient of the water peak was significantly higher than that of **2b**. However, when there were less than eight water molecules per six molecules of **2b**, the water diffusion coefficient was exactly the same as that of **2b** [37]. In the case of **3b**,

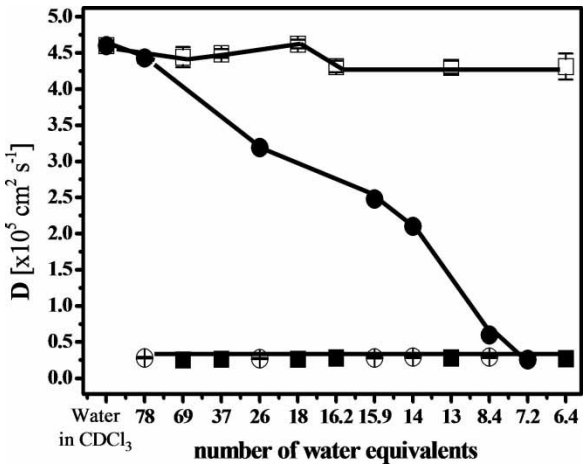

FIGURE 6 The effect of the macrocycle:water ratios on the diffusion coefficients of the macrocycles (■, ○) and the water (□, ●) in the $CDCl_3$ solution. The symbols (●, ○) and (■, □) represent the diffusion coefficients in the **2b** and **3b** systems, respectively.

however, the macrocycle:water ratio had no effect on the diffusion coefficients of the water molecules [39]. Based on these observations, we can conclude that in chloroform solution, **2b** forms a $[\mathbf{2b}_6(H_2O)_8]$-type hexamer whereas **3b** forms $\mathbf{3b}_6$-type hexamers. These results are in agreement with those found in the solid state [14–16]. It should be noted that the nature of R had no effect on the role played by the water molecules and both **2a** and **2b** form $[\mathbf{2}_6(H_2O)_8]$-type hexamers, whereas, **3a** and **3b** form $\mathbf{3}_6$-type hexamers [45]. Using the same methodology, we could demonstrate that when THABr, rather than chloroform molecules, is encapsulated in the hexamer of **2b** the water molecules are not present in the supramolecular structure and a $\mathbf{2b}_6$-type hexamer is formed [38]. The role played by the water molecules in the case of **2a** and **2b**, as obtained from diffusion NMR, is summarised in Fig. 7 [45, 46].

SELF-RECOGNITION IN THE SELF-ASSEMBLY OF HEXAMERIC CAPSULES

One of the peculiar characteristics of biological self-assembled systems is their sorting ability, and such self-sorting was also observed in some synthetic supramolecular systems [47–52]. Since, we found that **2a**, **2b**, **3a** and **3b** all form hexameric capsules, we studied their mixtures with the aim of establishing whether the self-assembly of these systems proceed with self-recognition within or across the macrocycle-types. The four possible mixture combinations of the above species, which differ sufficiently in their molecular weights, were studied.

Fig. 8 shows sections of the ^{1}H NMR spectra of **2a**, **2b** and their mixture as well as the diffusion coefficients measured for **2a** and **2b** with regard to the time that elapsed from the preparation of the mixture (Fig. 8(a) and (b), respectively). Fig. 8(c) and (d) shows the same type of data for **2a** and **3b**. These data clearly demonstrate the superiority of using diffusion coefficients as opposed to chemical shifts when studying the self-sorting in the self-assembly of such hexameric capsules [45, 46]. As shown in Fig. 8, the spectra of the mixtures are a mere superposition of the spectra of the individual compounds. Even after weeks, the ^{1}H NMR spectra of the mixtures remained the same with no clear indication of the formation of hetero-hexamers. However, the diffusion results were quite different for the mixtures studied. For example, in the mixture of **2a** and **2b**, different diffusion coefficients were observed, immediately after preparing the mixture, but they were found to equilibrate with time (Fig. 8(b)), thus indicating that hetero-hexamers are formed with time. However, different results were obtained for the mixture of **2a** and **3b**. In this case, the diffusion coefficients of these two compounds, which differ in their molecular weights, remained different. These results indicate that in a mixture of **2b**/**3a** or **2a**/**3b**, no hetero-hexamers could be detected even five weeks after preparing the mixtures. Therefore, we can conclude that the self-assembly of these hexameric capsules proceeds with self-recognition when mixtures of macrocycles of different types are prepared. However, in the case of compounds that differ only in their R group, i.e. within the macrocycle-type, hetero-hexamers are formed with time [45, 46].

GUESTS AND GUEST AFFINITY IN HEXAMERIC CAPSULES

As pointed out earlier, we found that systems **2** and **3** form hexameric capsules in a series of organic solvents, such as chloroform, benzene and methylene chloride. In these systems each of the hexameric capsules, encapsulate several solvent molecules. For compound **4**, which was investigated only recently and found to form hexameric capsules [40], we found discrete hexameric capsules only in chloroform and

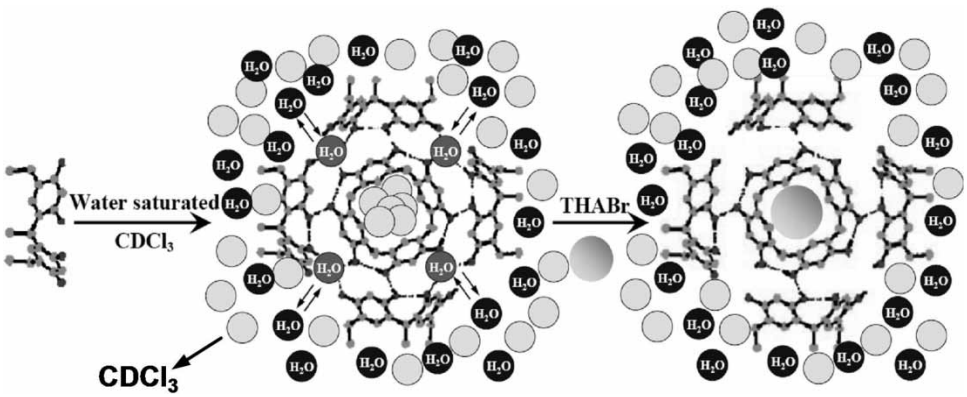

FIGURE 7 The role of water and the different water pools in the hexameric capsules of **2a** and **2b**. One of the hexameric building blocks was omitted for clarity.

in benzene but not in methylene chloride. These recent studies clearly demonstrate that the hexameric capsules of these systems are much more abundant structures in these types of solvents than previously thought [36–40, 45, 53].

In the last decade, hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes with various guests were reported in solution [17, 45, 53–60]. For example, hexameric capsules of **2b** with tetra ammonium salts and tertiary amines were reported [17, 45, 54–55]. In addition, **2b** was found to form hexameric capsules with diacids, sugars and other compounds [53–55]. In contrast, we found that **3b** encapsulates tertiary amines but not tetra ammonium salts. In fact, we showed that protonation of the tertiary amine in the capsule of **3b** resulted in the ejection of the protonated species from the capsules [54]. Furthermore, Kaifer's group demonstrated that **2b** and **3b** can encapsulate cobaltocenium cation [56]. During the last decade, hexameric capsule of pyrogallol[4]arenes with various guests were also prepared [57–60]. For compound **4**, we tested many classes of molecules as potential guests but only rarely were we able to observe an efficient encapsulation within this hexameric capsule. Despite the fact that capsules of resorcin[4]arenes and pyrogallol[4]arenes with different guests are now known to exist in solid, liquid and recently even in the gas phases [61], there seems to be no general rules at this point that can predict which guests will have high affinity to which hexameric capsules. In the following, we will conclude our short discussion on hexameric capsules by presenting the recent results for the capsules of **2b** with two specific guests, namely, glutaric acid (**6**) and methyl β-D-glucopyranoside (**7**), which demonstrate the new insights that can be obtained when diffusion NMR is used to study such systems [53].

Aoyama and co-workers reported that odd-numbered dicarboxylic acids, especially glutaric acid, form 1:1 host–guest complexes with **2b** where the two hydroxyls of the glutaric acid interact with two non-adjacent hydroxyls of **2b** [62]. Here again, the NMR peaks of the glutaric acid in the complex were shifted to high-field and a slow-exchange between glutaric acid in the bulk and in the complex was observed. Based on these observations, Palmer and Rebek have recently suggested that this might also be a hexameric capsule [63]. Indeed, recent diffusion measurements showed that the diffusion coefficient of this complex is very similar to that of the hexamer of **2b** with THABr and it was found to be $0.24 \pm 0.01 \times 10^{-5}\,\mathrm{cm^2\,s^{-1}}$ under the same experimental conditions ($CDCl_3$, 298 K, 20–30 mM;

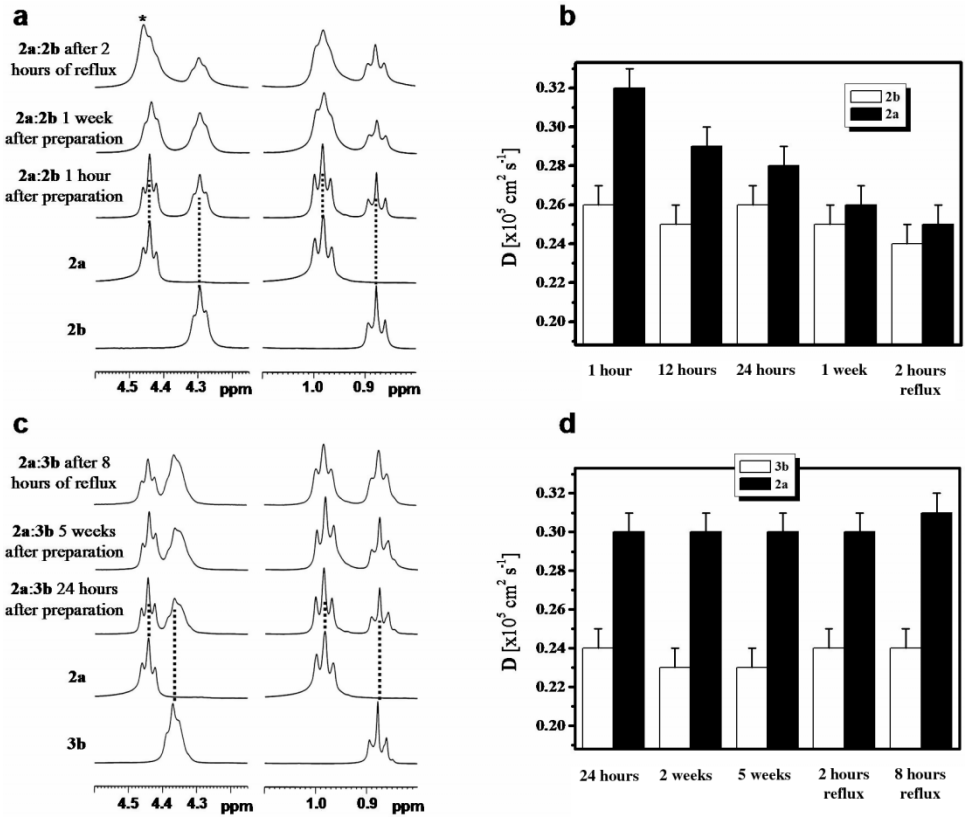

FIGURE 8 (a) Sections of the ^{1}H NMR spectra of **2a** and **2b** and their mixture and (b) the diffusion coefficients of **2a** and **2b** in $CDCl_3$ as a function of the time that elapsed since the preparation of the mixture; (c) and (d) show the same type of data, respectively, for a mixture of **2a** and **3b**.

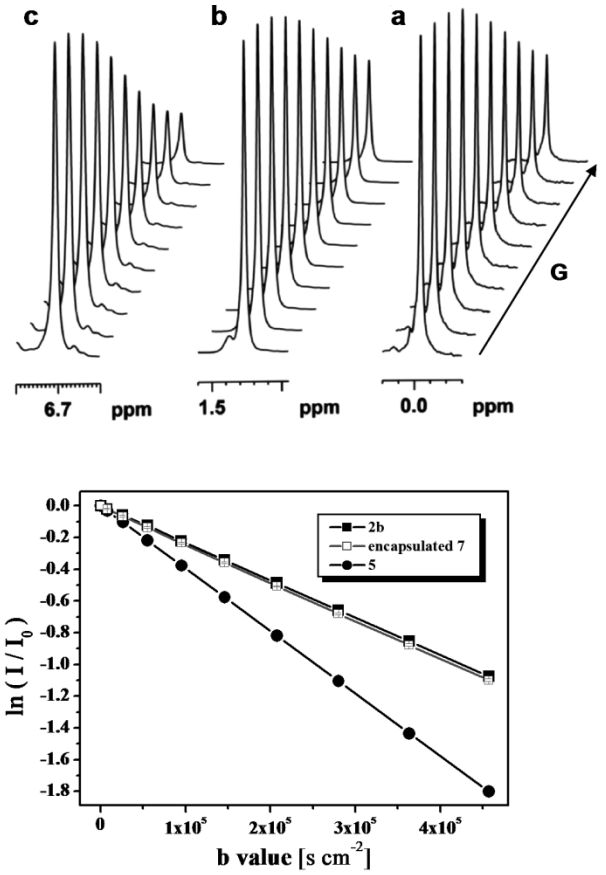

FIGURE 9 The stack plots of the signal decay as a function of *G* of a representative peak of (a) encapsulated **7**, (b) **2b** and (c) **5** in the same chloroform solution. (d) The signal decay as a function of the diffusion weighting (*b*-values) of the representative peaks shown in (a), (b) and (c).

[53]). Therefore, we could conclude that the 1:1 stoichiometry found for the complex of **2b** and glutaric acid is indeed a hexamer that encapsulates six molecules of glutaric acid molecules. In fact, we could show that when the addition of glutaric acid was followed by NMR in a $CHCl_3$ solution, the peaks at high-field shift attributed to the encapsulated glutaric acid molecules intensify at the expense of the peaks attributed to the encapsulated chloroform molecules [53].

However, a bigger challenge was determining the nature of the 2:1 stoichiometry complex of **2b** with **7**. Aoyama and co-workers suggested the formation of a dimeric capsule with **7** based on the integration of the NMR peaks [64,65]. Since a dimeric complex of **2b** with **7** was suggested, we performed the diffusion NMR measurements with compound **5** as an internal reference. Compound **5** has a molecular weight (2398 g mol^{-1}) very similar to that of the dimer of **2b** (2208 g mol^{-1}). It was important to verify whether, under the same experimental conditions (solvent, temperature and concentration), the 2:1 complex of **2b** with **7** has a much lower diffusion coefficient as compared with compound **5**.

Fig. 9, which presents the stack plots of the signal decay of a representative peak of **5**, and of **2b**, and **7** in their 2:1 complexes (taken from the same measurement) as well as the signal attenuation of these peaks as a function of the diffusion weighting (*b*-values) shows that this is indeed the case.

The diffusion coefficients of both **2b** and **7** were found to be much lower than those of compound **5**, as expected for the hexameric capsule of **2b**. Once again, the diffusion coefficient of the capsules of **2b** with **7** was found to be exactly the same as that of the hexameric capsule of **2b** with THABr, for example. Therefore, we concluded that the 2:1 stoichiometry represents a hexameric capsule with three encapsulated sugar molecules [53].

CONCLUSIONS

We have demonstrated, with the aid of diffusion NMR that systems such as **2**, **3** and **4** self-assemble spontaneously into hexameric capsules in organic solvents. Many of the previously characterised complexes of resorcin[4]arenes and pyrogallol[4]arenes are, in fact, hexameric capsules. Diffusion NMR was found to be very useful in determining the role of water molecules in the self-assembly of such capsules. Importantly, we can determine when the self-assembly of such hexameric capsules proceed with or without self-recognition and self-sorting. In addition, we have demonstrated the added value of diffusion NMR when such structures are characterised in solution. Aggregates that have the same symmetry as their monomer can easily be identified with diffusion NMR. Therefore, we conclude that diffusion NMR is a powerful tool for studying supramolecular systems and self-assembly in solution.

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