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Received December 3, 2007

ABSTRACT

We followed the self-assembly of C-alkyl-resorcin[4]arene (1a,1b) in the presence of tetraethylammonium salts (2). The X-ray structure of C-ethyl-resorcin[4]arene (1c) in the presence of TEABr (2b), showed a dimer encapsulating one guest. However, diffusion measurements reveal that two molecules of tetraethylammonium are encapsulated within the hexameric capsule of 1a,b in chloroform, regardless of the anion. Most importantly, the anion affects the role of water in the self-assembly and the nature of the formed capsules.

The study of hydrogen-bonded molecular capsules has progressed rapidly over the past decade.1-9 Both dimeric1-4 and hexameric1,5-9 hydrogen-bond capsule have been investigated in the solid state5 and in solution.6-9 Recently, we have shown, by diffusion NMR, that different resorcin[4]arenes and pyrogallol[4]arenes self-assemble spontaneously into hexameric capsules in a series of organic solvents.6

Hexameric capsules of resorcin[4]arenes and pyrogallol[4]arenes with various guests were also reported in solution.7,8 However, the guest affinity of these systems and the effect of guest molecules on the structure of the formed supramolecular complexes remain elusive.

Diffusion NMR has become an important technique for studying the self-assembly of supramolecular systems in solution.10 It was shown that diffusion NMR is a powerful tool for probing encapsulation,11 and the self-assembly of...
resorcin[4]arene (1), pyrogallol[4]arene (4), and octahydroxy-

Recently, the self-assembly of 1a in the presence of relatively small guests, such as glacial acid (6) and β-methyl-β-glucopyranoside (7) was studied by diffusion NMR.7b Aoyama and co-workers claimed that 1a forms 1:1 and 2:1 complexes with 6 and 7, respectively. However, diffusion NMR studies showed that 1a forms hexameric capsules which encapsulate six and three molecules of 6 and 7, respectively.7b These examples demonstrate the new insights that can be obtained when using diffusion NMR to study such systems.7b

Here, we used diffusion NMR to study the self-assembly of resorcin[4]arenes (1a and 1b) in the presence of small guests, i.e., tetraethylammonium salts (2). Calculations and X-ray structures indicated that these guests are encapsulated in dimeric capsules of C-ethyl resorcin[4]arene (1c).14,15a It was also stated that, according to the 1H NMR spectrum of 1a and triethylammonium bromide, a dimer is formed in a CDCl₃ solution, which encapsulates one molecule of this salt.15b However, the diffusion data, acquired in chloroform solutions, show otherwise.

First, we examined the encapsulation of tetraethylammonium bromide (TEABr 2b). When TEABr (2b) was added to the solution of 1a, new signals appeared at δ −0.1 and 1.7 ppm, as was previously reported for triethylammonium bromide (Figure 1). These peaks were previously attributed to the encapsulated salt inside the cavity of the dimeric capsules.15a We repeated these experiments for all the other tetraethylammonium guests, and in all cases these new signals appeared at high field (Figure 1). We could not observe the signals of free guest molecules for all the different salts. According to the integration the ratio between 1a and the new peaks of 2a−f was 3:1 (data for 2f are not shown). This is a very odd ratio since it indicates the formation of a trimer with one guest molecule or a hexamer with two guest molecules, and both these options were not suggested before for these systems. It should be noted that in a recent study Palmer et al. suggested that the high-field peaks observed when TEACl (2a) is added to 1a may well represent three cations per hexamer or one cation within a dimeric capsule.15b To determine which of these aggregates is the main species in this chloroform solution we turned to diffusion NMR.10

Figure 1. 1H NMR spectra (400 MHz, 298 K) of 1a in CDCl₃ in the presence of different tetraethylammonium salts (2a−e). The asterisk indicates the water peak and ▲ indicates the peaks of the encapsulated salts.

The diffusion coefficients of 1a and the encapsulated salts 2a−f, shown in Figure 2, were found to be very similar (0.24 ± 0.01 × 10⁻⁵ cm² s⁻¹ 298 K, CDCl₃, 20 mM). These findings are reasonable since the encapsulated guest and the host diffuse as a single entity; thus, they must have the same diffusion coefficient. This value is consistent with the diffusion coefficient of a hexameric capsule of 1a with

Figure 2. Diffusion coefficients of the peaks of 1a, different encapsulated ammonium salts in the hexamers of 1a and biscalix[5]arene (3). Compound 3 has a molecular weight of 2398 g mol⁻¹, which is slightly higher than the molecular weight of the dimer of 1a.


tetrahexylammonium bromide (THABr) (Figure 2),\textsuperscript{5a,16} and is also very similar to that previously obtained for the hexameric capsules of pyrogallo[4]arene (\textit{4a})\textsuperscript{6c,d} and octahydroxypyridine[4]arene (Opy, \textit{5}).\textsuperscript{9} The diffusion coefficients of \textit{1a} with 2a–f are significantly lower than that of a biscalix[5]arene (3),\textsuperscript{17} having a molecular weight of 2398 g mol\textsuperscript{−1}, which is slightly larger than that of the dimer of \textit{1a} (Figure 2).

Since the values that were extracted for \textit{1a} and the encapsulated tetraethylammonium guests were very similar to those obtained for the hexameric capsules of \textit{1a}, \textit{4a},\textsuperscript{6c,d} and \textit{5},\textsuperscript{9} we concluded that \textit{1a} self-assembles into a hexameric capsule even in the presence of small guests such as tetraethylammonium salts. Two molecules of the tetraethylammonium seem to be encapsulated within the hexameric capsule of \textit{1a}, regardless of the anion of these salts. These results indicate that the self-assembly of this supramolecular system in chloroform solution is very much different from the dimeric structure found in the solid state.\textsuperscript{14} Interestingly, we found exactly the same behavior for host 1b. We found diffusion evidence only for hexameric capsules of 1b with the studied salts (see Figures S1–S3 in the Supporting Information). Here, again, two tetraethylammonium molecules are encapsulated in each hexameric capsule.

It was shown that in systems where exchange and NOE interactions between nuclei that differ considerably in their diffusion coefficients exist, the signal decay extracted from pulsed gradient spin echo (PGSE) and pulsed gradient stimulated echo (PGSTE) diffusion sequences is monoexponential, whereas the signal decay extracted from the longitudinal eddy current delay (LED) and bipolar longitudinal eddy current delay (BPLED) diffusion sequences is not.\textsuperscript{18} Therefore, we suggested that, in the present systems, non-monoexponential signal decay in the LED and BPLED experiments can serve as a good indication of exchange or NOE interactions between sites that differ in their diffusion coefficients.\textsuperscript{18}

We decided to examine the role of water in the self-assembly of \textit{1a} in the presence of the different salts (2a–e). Previously it was found, by diffusion NMR, that \textit{1a} self-assembles into a hexameric capsule with eight water molecules.\textsuperscript{6b} However, after the addition of THABr, \textit{1a} encapsulates the salt and forms a hexameric capsule, where the water molecules are no longer part of the supramolecular structure.\textsuperscript{16} We assumed that, owing to the $\pi$–cation interactions, THABr acts as a pseudotemplate for the self-assembly of the hexameric capsule of \textit{1a} and that the assistance or the mediation of the water molecules is, therefore, less needed.\textsuperscript{16} For this reason, we expected to find the same results for 2a–e. However, when we measured the signal decay of the water peak in the CDCl$_3$ solutions of \textit{1a} and 2a and 2c–e, by using the LED sequence surprising results were obtained, as shown in Figure 3.

Figure 3 shows that, although the same signal decay is observed for the peak of \textit{1a} in all the different samples (Figure 3A–E), the signal decay of the water peak, in the presence of the different salts, differs dramatically (Figure 3F–J). Apparently, the water signal decay in the presence of 2a and 2c is monoexponential (Figure 3H and I, respectively), like that found for water in the presence of THABr\textsuperscript{16} (Figure 3J), where water molecules are not part of the hexameric capsule. However, in the presence of 2d and 2e an extra slow diffusion component is observed only for the water peak (Figure 3G and F, respectively). Therefore, we suspected that, although \textit{1a} forms hexameric capsules in the presence of 2a–f that encapsulate two guest molecules, these capsules are not exactly the same for all the different anions.

We have previously shown that the additional extra diffusion component of the water signal develops during the eddy current delay (the $t_e$ period) of the LED and BPLED sequences.\textsuperscript{18} As this delay was increased, the extra component of the water signal decay became more pronounced.\textsuperscript{18} To verify the reason for the difference in the water signal decay, we examined the effect of $t_e$ on the water signal decay in the presence of two different salts: TEACl (2a) (Figure 4B–D) and TEABF$_4$ (2d) (Figure 4F–H). We also compared these water signal decays to those extracted from the PGSTE diffusion sequence, in which this delay does not exist and only monoexponential signal decay is expected (Figure 4A and E).

The signal decay of \textit{1a} was not affected by the different pulse sequences or by the increase in the $t_e$ delay (see Figures

With the LED sequence with a $t_e$ of 5 ms, the same water signal decay was observed for both salts. This indicates that, indeed, by using a relatively short $t_e$, the LED sequence is degenerated into a PGSTE-like sequence and no bending in the water signal decay is observed. For 2a, only for very long $t_e$’s, could some deviation from linearity be observed. This is probably due to some exchange between the water molecules and the OH moieties on the aromatic rings of 1a. However, for 2d the effect of increasing the $t_e$ on the water signal decay is much more significant. The additional extra diffusion component of the water signal can be observed for a $t_e$ as short as 50 ms, which increases significantly for a $t_e$ of 150 ms. These results indicate that exchange between the different populations of the water molecules is much more pronounced for the solution of 1a in the presence of 2d than in the presence of 2a.

All these results indicate that the role of water in the self-assembly of 1a, in the presence of different tetraethylammonium salts, differ when different anions are used. Apparently, when the anion is a halide such as in 2a, 2b, and 2c, there are no water molecules that are part of the supramolecular system of the capsule, as was found for THABr.$^{16}$ These salts are sufficient to induce the formation of the hexameric capsule of 1a, and there is no need for a significant number of water molecules in order to construct the supramolecular capsule. However, when the anion is BF$_4^-$ or PF$_6^-$, the effect of $t_e$ on the water signal decay is exactly as that obtained for water in a solution of 1a in the absence of any salt, as demonstrated in Figure 5. Since the effect of $t_e$ is the same both in the presence and absence of 2d or 2e, it is reasonable to assume that the role of the water molecules in the self-assembly of 1a in these systems is the same. Therefore, we can conclude that in the presence of either 2d or 2e, 1a self-assembles into [1a$_6$(H$_2$O)$_8$]-type capsules that encapsulate two guest molecules, while in the presence of 2a–c, 1a self-assembles into a hexameric capsule without water molecules. The same results were also obtained for 1b, (see Figure S3 in the Supporting Information).

In conclusion, diffusion NMR shows that 1a and 1b form hexameric capsules in chloroform solutions in the presence of different salts, even though dimeric capsules are found in the solid state. In addition, two molecules of the tetraethylammonium guests seem to be encapsulated within each hexameric capsule, regardless of the anion of these salts. However, we found that the role of water molecules in the self-assembly of 1a and 1b with TEAX is different for different anions. In the presence of 2a–c, 1a forms a [1a$_6$]-type capsule, whereas with 2d and 2e, 1a forms a [1a$_{10}$-(H$_2$O)$_3$]-type capsule. The same results were also obtained for 1b.

**Acknowledgment.** This research was supported by The Israel Science Foundation (ISF, Grant No. 301/07).

**Supporting Information Available:** $^1$H and $^{13}$C NMR data of the hexamers of 1a and 1b; Figures S1–S3 showing the same data as that shown in Figures 1–3 for C-isobutylresorcine[4]arene (1b). Figures S4 and S5 show the effect of $t_e$ on the signal decay of 1a and water in the presence of TEACl (2a) and TEABF$_4$ (2d), respectively.

OL702912U