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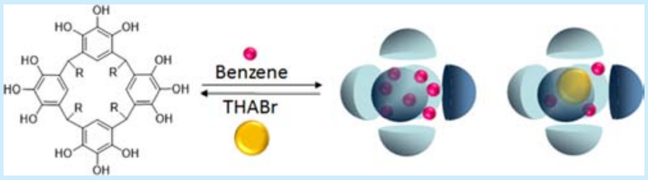
# Encapsulated or Not Encapsulated? Ammonium Salts Can Be Encapsulated in Hexameric Capsules of Pyrogallol[4]arene

Shani Yariv-Shoushan and Yoram Cohen*

School of Chemistry, The Sackler Faculty of Exact Sciences, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel

Supporting Information

**ABSTRACT:** Tetraalkylammonium salts were found, contrary to literature reports, to be encapsulated into hexameric capsules of pyrogallol[4]arene in benzene solution. The guest affinity depended on the length of the alkyl chain, the counteranion, the solvent used, the ammonium concentration, and most importantly, the pyrogallol[4]arene to ammonium salt ratio. At high ammonium salt to pyrogallol[4]arene ratios no encapsulation was observed, presumably since the high salt destabilized the formed hexamers.



The Atwood and Mattay groups found that resorcin[4]arenes (**1a**, Figure 1) and pyrogallol[4]arenes (**1b**) form hexameric capsules in the solid state.[1,2] In 2001, Shivanyuk and Rebek[3] reported on the first encapsulation of ammonium guests by the hexameric capsule of **1a** in water-saturated $CDCl_3$ solutions. Later, Avram and Cohen showed, using diffusion NMR, that such systems self-assemble spontaneously into hexameric capsules in organic solvents.[4] These studies changed the way we conceive of the structures of such systems and demonstrated that hexameric capsules are more abundant and stable, in solution, than previously thought.[5]

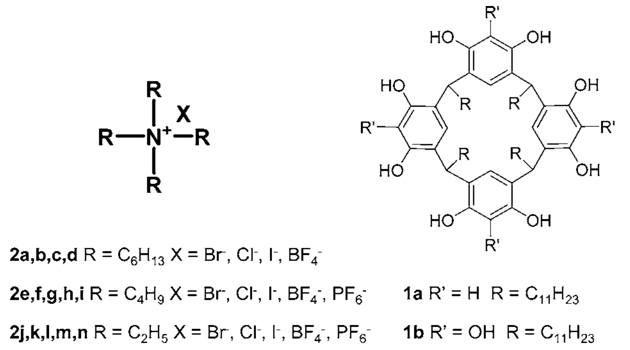


**Figure 1.** Chemical structures.

Despite the apparent similarity between the resorcin[4]arene and pyrogallol[4]arene hexameric capsules, it was found that their self-assembly proceeds with narcissist self-sorting,[4d,6] probably due to the fact that **1a** and **1b** form $\mathbf{1a}_6(H_2O)_8$- and $\mathbf{1b}_6$-type capsules, respectively.[4] Additional striking differences between the **1a** and **1b** hexameric capsules are the much more structured $^1H$ NMR signals of the encapsulated solvent molecules[7] in $\mathbf{1b}_6$ as compared to $\mathbf{1a}_6(H_2O)_8$ and the fact that the hexamers of **1a** were found to encapsulate a much larger repertoire of guests than do $\mathbf{1b}_6$.[8,9] This may be one of the reasons that all examples of supramolecular catalysis in these hexameric capsules described thus far are in the resorcin[4]arene hexamers rather than the pyrogallol[4]arene hexamers.[10] In addition, in chloroform solution, $R_3N$ and $R_4N^+$ are encapsulated in **1a** hexamers, whereas only $R_3N$ are encapsulated in the **1b** hexamers.[11] However, guest affinity toward the capsule's cavity in solution may be masked by the solvent affinity. The very structured $^1H$ NMR spectra for the encapsulated solvent molecules seems to suggest that the solvent affinity for the **1b** capsule cavity is significant.

On the basis of these observations and on the fact that the hexamer of **1b** is formed without the aid of water molecules, the Purse group speculated that a solvent-free method, the melting approach, should enable one to increase the repertoire of guests that can be encapsulated in the hexameric capsules of **1b**.[12] Indeed, it was found that many guests that could not be encapsulated when chloroform was used as a solvent were encapsulated in the hexameric capsule of **1b** when the melting method was used.[12] In these recent studies, it was found that tetraalkylammonium salts ($R_4N^+X^-$) are not encapsulated in the hexamers of **1b**. This suggested that the low affinity of $R_4N^+X$ for the cavity of $\mathbf{1b}_6$ is apparently an intrinsic characteristic of the system.

When studying xenon encapsulation in hexameric capsules of **1b** in benzene, we added tetrahexylammonium bromide (THABr) to increase the ionic strength of the bulk solution with the aim of increasing xenon encapsulation in the hexameric capsule of **1b**. In contrast to our expectations, evidence for THABr encapsulation was obtained. Therefore, we decided to systematically study the encapsulation of different $R_4N^+X^-$ salts in the hexamer of **1b** in benzene solutions and other solvents (**2a**−**n**, Figure 1). Figure 2 shows the $^1H$ NMR spectra of $\mathbf{1b}_6$ in benzene-$d_6$ and in the presence of several $R_4N^+Br^-$ guests having different alkyl chain lengths. The signals at high field in these spectra and the diffusion coefficients

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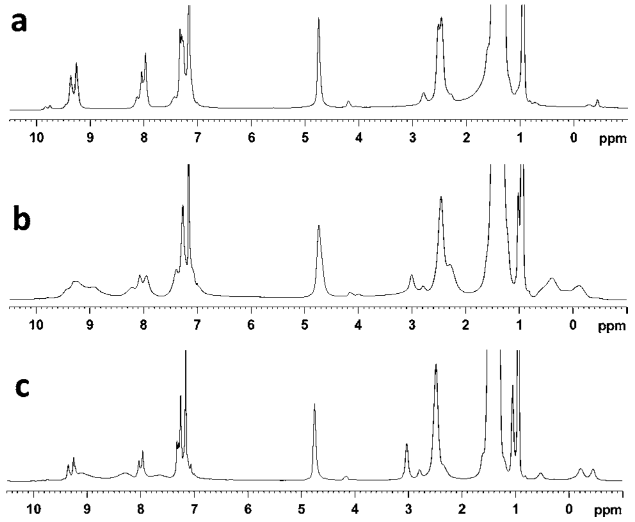

**Figure 2.** $^1H$ NMR spectra (500 MHz, 298 K) of 50 mM **1b** in benzene-$d_6$ after addition of 17 mM of (a) tetraethylammonium bromide (TEABr), (b) tetrabutylammonium bromide (TBABr), and (c) THABr.

measured show that the different $R_4N^+$ salts were indeed encapsulated in the hexamers of **1b**. The amount of encapsulation appeared to be dependent on the length of the alkyl chains. Importantly, when such experiments were repeated in other organic solvents including $CHCl_3$ and $CH_2Cl_2$ (see Figure S1, Supporting Information (SI)), no significant encapsulation was observed under the same experimental conditions. These results demonstrate that significant encapsulation of these symmetrical tetraalkylammonium guests occurs mainly in benzene solution.

Since we previously observed a significant effect of the counteranion on the spectroscopic characteristics of the hexamer of **1a**,[8g] we examined the $^1H$ NMR spectra of 50 mM **1b** in benzene in the presence of 17 mM tetraethylammonium (TEA), tetrabutylammonium (TBA), and tetrahexylammonium (THA) salts having various counteranions (Figure 3). In the case of the large THA salts, only the chloride and bromide salts were encapsulated (Figure 3a–d), whereas in the case of the smaller TBA salts the iodide and trifluoroborate salts were encapsulated in addition to the chloride and bromide (Figure 3e–h). In the case of $TBAPF_6$, however, no encapsulation was observed (Figure 3i). For the small TEA salts, all salts were found to be encapsulated, even, to some degree, the $TEAPF_6$ salt (Figure 3j–n). The complete $^1H$ NMR spectra of each of these solutions are presented in (Figures S2–S4, SI). Our data clearly demonstrate that when less bulky ammonium cations are used, salts with bulkier anions can be encapsulated by the hexamer of **1b**. These results suggest that the salts are encapsulated as ion pairs in $\mathbf{1b}_6$.

Since the encapsulation of the symmetrical ammonium salts was more favorable in benzene than in other solvents, the 3:1 ratio of **1b** to $R_4N^+$ appeared optimal for encapsulation, and THABr appeared to be a good guest for $\mathbf{1b}_6$ in benzene, dilution experiments were performed on samples of **1b** and THABr. We observed a decrease in the amount of encapsulated THABr upon dilution as shown in Figure S5 in the SI. When the **1b** and THABr concentrations were 10 and 3 mM, respectively, there was no evidence for significant encapsulation of the ammonium salt in the hexamer of **1b**.

Next, we explored the effect of the **1b**/$R_4N^+$ ratio on the efficiency of the ammonium salt encapsulation. Here again, we used THABr as a representative salt. $^1H$ NMR spectra were collected in benzene and are presented in Figure 4 and Figure S6. We examined **1b**/$R_4N^+$ ratios of 3:1, 3:2, 1:1, 2:3, and 2:4 with a concentration of **1b** of 50 mM. When the **1b**/THABr ratio was 3:1, high-field peaks were observed accompanied by a significant peak due to the encapsulated benzene (Figure 4a and Figure S6a). At 3:2 and 1:1 **1b**/THABr ratios, the high-field signals of the encapsulated salt were observed, and those of the encapsulated benzene appeared significantly less intense than at the 3:1 ratio. For the solutions where the **1b**/THABr

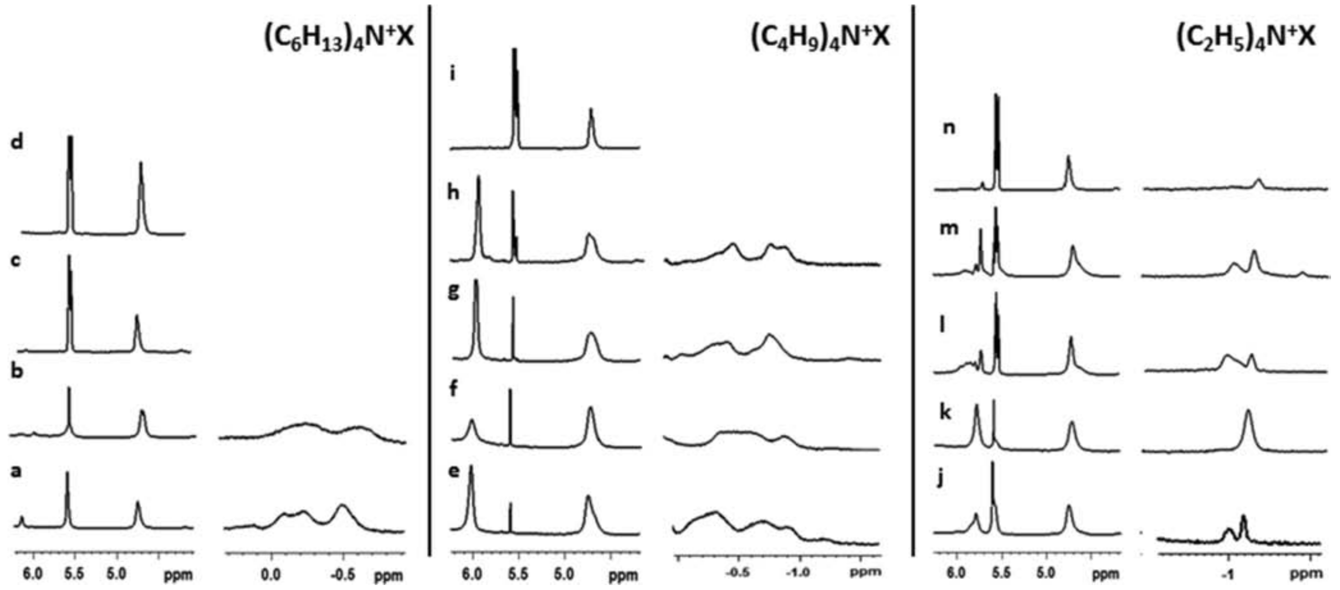

**Figure 3.** Extracts of $^1H$ NMR spectra (400 MHz, 298 K) of 50 mM benzene solutions of **1b** showing chemical shift regions corresponding to the encapsulated benzene and the encapsulated ammonium salts (a) X = $Br^-$, (b) X = $Cl^-$, (c) X = $I^-$, (d) X = $BF_4^-$, (e) X = $Br^-$, (f) X = $Cl^-$, (g) X = I, (h) X = $BF_4^-$, (i) X = $PF_6^-$, (j) X = $Br^-$, (k) X = $Cl^-$, (l) X = $I^-$, (m) X = $BF_4^-$, (n) X = $PF_6^-$. For the entire $^1H$ NMR spectrum for each sample, see Figures S2–S4 in the SI.

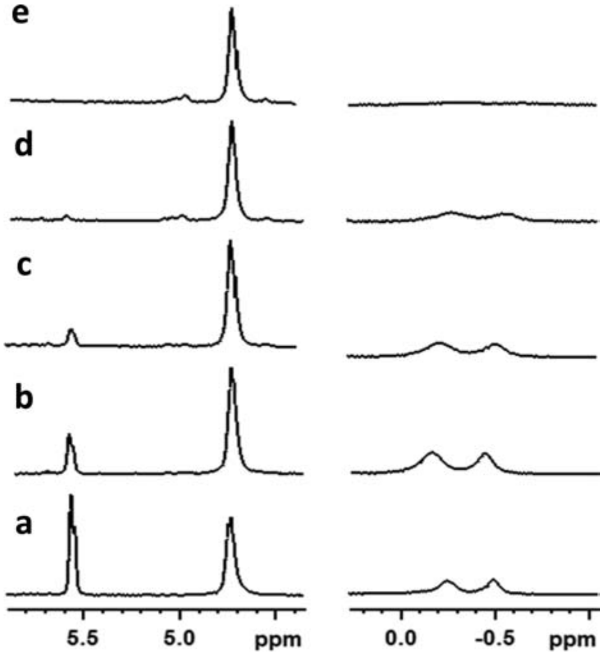

**Figure 4.** $^1$H NMR spectra (500 MHz, 298 K) of 50 mM solution of **1b** in benzene in the presence of THABr at (a) 17 mM, (b) 34 mM, (c) 50 mM, (d) 75 mM, and (e) 100 mM. All signals at high field are scaled to the peak of **1b** at 4.8 ppm.

ratios were 2:3 and 1:2, however, no signals for the encapsulated salt were observed, and even the signals at ~5.5 ppm attributed to encapsulated benzene disappeared from the spectra. These results may suggest that no hexameric capsules are present in the solution under these experimental conditions. To further verify this issue, we reverted to diffusion NMR,[13] which has been shown to be an extremely useful tool for probing the formation and existence of capsules in solutions.[4,14] In the solution of 50 mM **1b** and 17 mM THABr (3:1 ratio benzene) presented in Figure 4a, we found that the diffusion coefficients ($D$) of the capsule, the encapsulated THABr, and the nonencapsulated THABr were $0.22 \pm 0.01 \times 10^{-5}$ cm$^2$/s (Table S1). These results suggest that when there are about two molecules of THABr per hexamer one molecule is indeed encapsulated but the other THABr molecule which is not encapsulated is in fact tightly bound to the exterior of the hexamer. Under these experimental conditions, the hexamers and the two THABr molecules diffuse as a single supramolecular entity as was found previously for the resorcin[4]-arene hexamers.[15] Diffusion measurements of the sample with a **1b**/THABr ratio of 2:4 yielded nearly the same diffusion coefficients as in the case of the 3:1 ratio (Table S1). These results suggest that when there is an excess of the ammonium salt the disappearance of the signals of the encapsulated guests is probably due to the increased exchange between the encapsulated guest and the guest in the bulk rather than disruption of the hexameric structure.

In conclusion, we have demonstrated that, contrary to literature reports, tetraalkylammonium salts can, in benzene solution, be encapsulated into the hexameric capsules of **1b**. The fact that shorter chain $R_4N^+$ salts were encapsulated in the presence of bulkier counteranion implies that salts are encapsulated as ion pairs. We found that for the $R_4N^+$ salts tested, encapsulation depends on the solvent used, the concentration, and the nature of the salt (cation and anion). Significant encapsulation was found only in benzene solutions, and the most crucial parameter that affected encapsulation was the **1b** to salt ratio. At high salt concentrations, the signals of the encapsulated ammonium salts disappear. Diffusion NMR experiments showed that an excess of ammonium salt apparently destabilizes the hexamers, thus increasing the exchange between the encapsulated guest and the guest in the bulk. At the **1b**/salt ratios tested it seems that the hexamers, although destabilized, are still present in the solution.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03655.

General experimental procedures, $^1$H NMR spectra of the different solutions studied, and table of diffusion measurements (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: ycohen@post.tau.ac.il.

### Notes

The authors declare no competing financial interest.

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