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Effect of a Cationic Guest on the Characteristics of the Molecular Capsule of Resorcinarene: A Diffusion NMR Study

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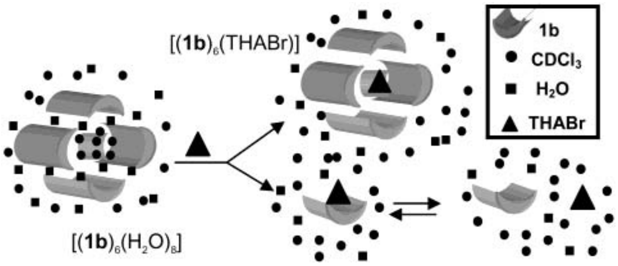
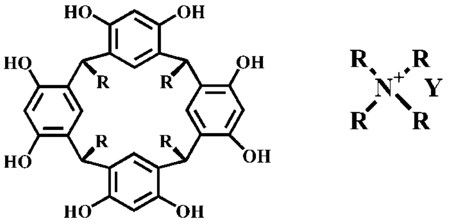
ABSTRACT



NMR diffusion measurements were used to probe the differences in the characteristics of the hexameric capsule of [c]-undecane resorcin[4]arene (1b) in a CDCl$_3$ solution in the absence and presence of tetrahexylammonium bromide (THABr). It was found that the nonencapsulated THABr forms a 1:1 complex with 1b, which is in fast exchange with its constituents. We found that water molecules seem not to participate in the construction of the THABr hexameric capsule of 1b in a CDCl$_3$ solution, in contrast to the finding in the absence of THABr, where the major species in CDCl$_3$ seems to be [(1b)$_6$(H$_2$O)$_8$].

Hydrogen-bond molecular capsules[1,2] have attracted considerable attention in recent years due to the pioneering contributions of the groups of Rebek and Böhmer.[1−3] Atwood and his group demonstrated that resorcin[4]arenes such as those shown in Scheme 1 form large capsules with large cavities.[4] These large molecular capsules are generally assembled from a multiplicity of molecules held together by weak noncovalent bonds. Atwood found that resorcinarene **1a**, for example, self-assembles in the solid-state to a hexameric capsule of the ($\mathbf{1a}$)$_6$(H$_2$O)$_8$-type.[4] In addition, Rebek and Shivanyuk demonstrated that **1b** forms a stable hexameric capsule with suitable guests in a water-saturated chloroform solution.[5] Recently, we demonstrated, with the aid of diffusion NMR, that **1b** in fact forms a hexameric capsule in a water-saturated CDCl$_3$ solution by encapsulating several chloroform molecules.[6a] We were also able to demonstrate that water molecules play a crucial role in the

Scheme 1



1a R=CH$_3$
1b R=C$_{11}$H$_{23}$

2: R=Hexyl
Y=Br$^-$

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[1] For a few early examples of dimeric hydrogen-bond capsules, see: (a) Shimizu, K. D.; Rebek, J. Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403−12407. (b) Hamann, B. C.; Shimizu, K. D.; Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329. (c) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534. (d) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712.

[2] For a few recent examples of hydrogen-bond capsules, see: (a) Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J. Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640−1644. (b) Vysotsky, M. O.; Böhmer, V. *Org. Lett.* **2000**, *2*, 3571−3573. (c) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264−1267. (d) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Chem. Commun.* **2001**, 1890−1891.

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construction of this molecular capsule in the water-containing $CDCl_3$ solutions. We found, using diffusion NMR, that eight water molecules seem to participate in the construction of the hexameric capsule.[6b] Recently, Philip and Kaifer demonstrated that ferrocenium ion is a much better guest toward the cavity of the hexamer of **1b** than ferrocene,[7] which is in line with previous studies that demonstrated the relative importance of cation−π interactions in determining the affinity of the guests toward the cavity of such a molecular capsule.[8]

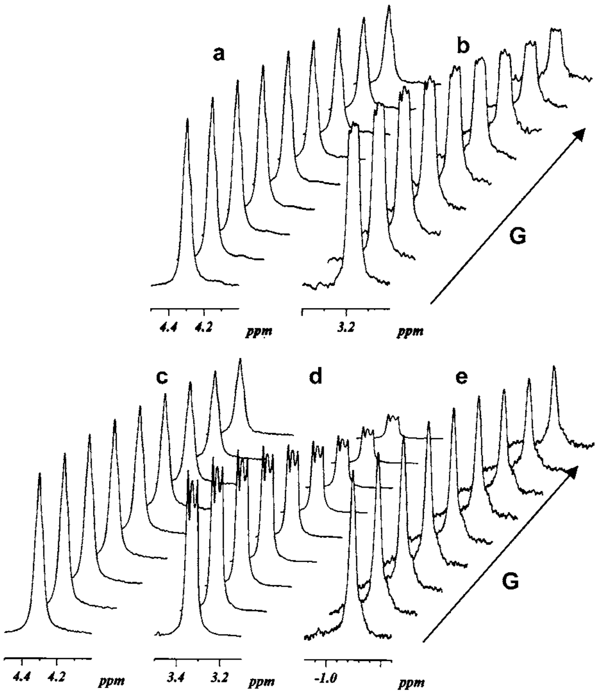

Figure 1. ^{1}H NMR signal decay as a function of the gradient strength (*G*) (400 MHz, 298 K) of **1b** (a and c), nonencapsulated THABr (b and d), and encapsulated THABr (e) in $CDCl_3$ solutions when the **1b**/THABr ratios were 6:1.26 (a and b), and 6:8.02 (c−e).

It was found that **1b** forms hexameric capsules in water-containing $CDCl_3$ solutions both in the presence and absence of a cationic guest.[5,6] Since we found that the same amount of DMSO-d_6 is required to disrupt these hexamers, although the affinity of the cationic guest toward the hexameric cavity is clearly several orders of magnitude higher than that of the $CDCl_3$ molecules,[6a] we decided to further explore these two capsules and evaluate the effect of the cation on the structure and the involvement of water molecules in the formation of such hydrogen-bond hexameric capsules by NMR diffusion measurements.[9] NMR diffusion measurements can be used to probe complexation, aggregation, and ion pairing and may be used to study intermolecular interactions in general.[10] Recently, we demonstrated that this method is extremely useful in monitoring encapsulations.[8b,11]

First, we prepared a sample of **1b**[12] in $CDCl_3$ that we titrated with different amounts of tetrahexylammonium bromide (THABr **2**). Figure 1 shows stack plots of sections of the ^{1}H NMR spectra of **1b** and THABr in $CDCl_3$ solutions at 298 K at two different **1b**/THABr ratios. Figure 1 shows that with the increase in the amount of THABr there is an increase in the diffusion coefficient[13] of the nonencapsulated THABr.

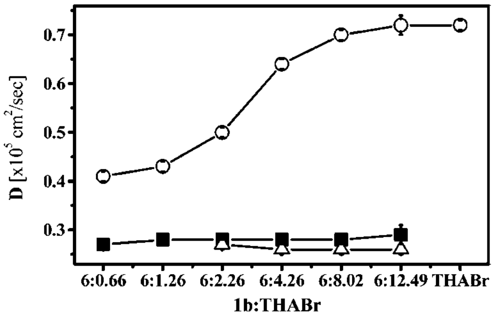

Figure 2. Diffusion coefficients (×10^5) of **1b** (■), nonencapsulated THABr (○), and encapsulated THABr (△) as a function of the **1b**/THABr ratio.

Figure 2 shows the diffusion coefficients of **1b**, the nonencapsulated THABr, and the encapsulated THABr as a function of the change in the **1b**/THABr ratio. This Figure shows that both **1b** and the encapsulated THABr have a low, constant, and very similar diffusion coefficient. However, the diffusion coefficient of the nonencapsulated THABr increases gradually when THABr is added to the solution, reaching the value of free THABr when there is a large excess of THABr. The only explanation for the above results

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(3) For recent reviews concerning hydrogen-bond capsules, see: (a) Rebek, J. Jr. *Chem. Commun.* **2000**, 637−643. (b) Böhmer, V.; Vysotsky, M. O. *Aus. J. Chem.* **2001**, *54*, 671−677. For general reviews on encapsulation, see: (c) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509−518. (d) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J. Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508.

(4) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469−471.

(5) (a) Shivanyuk, A.; Rebek, J. Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662−7665. (b) Shivanyuk, A.; Rebek, J. Jr. *Chem. Commun.* **2001**, 2424−2425.

(6) (a) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148−15149. (b) Avram, L.; Cohen, Y. *Org. Lett.* **2002**, *4*, 4365−4368.

(7) Philip, I. E.; Kaifer, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 12678−12679.

(8) (a) Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J. Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568−4579. (b) Frish, L.; Vysotsky, M. O.; Matthews, S. E.; Böhmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **2002**, 88−93.

(9) (a) Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *42*, 288−292. (b) Tanner, J. E. *J. Chem. Phys.* **1970**, *52*, 2523−2526. For a review concerning the application of the PGSE NMR technique, see: Stilbs, P. *Prog. NMR Spectroscopy* **1987**, *19*, 1−45.

(10) For a few selected examples, see: (a) Rymdén, R.; Carlfors, J.; Stilbs, P. *J. Inclusion Phenom.* **1983**, *1*, 159−167. (b) Mayzel, O.; Cohen, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1901−1902. (c) Prochapsky, S. S.; Mo, H.; Prochapski, T. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2513−2514. (d) Mayzel, O.; Gafni, A.; Cohen, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 911−912. (e) Gafni, A.; Cohen, Y. *J. Org. Chem.* **1997**, *62*, 121−126. (f) Valentini, M.; Rügger, H.; Pregosin, P. S. *Helv. Chim. Acta* **2001**, *84*, 2833−2853. (g) Avram, L.; Cohen, Y. *J. Org. Chem.* **2002**, *67*, 2639−2641.

(11) Frish, L.; Matthews, S. E.; Böhmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 669−671.

(12) Compound **1b** was synthesized according to: Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−1312.

Table 1. Effect of the **1b**/THABr Ratio on the Diffusion Coefficient of **1b**, the Non-encapsulated THABr and the Encapsulated THABr at 298 K

system[a] **1b**/non-encapsulated **2** ratio **1b**/encapsulated **2** ratio	non-encapsulated **2** chemical shift	diffusion coefficients [$\times 10^5$ cm^2/sec]		
		1b 1.3 ppm	non-encapsulated **2**	encapsulated **2**
2 in $CDCl_3$	3.39 ppm		0.76 ± 0.01 0.72 ± 0.01[b]	
1b:**2** 6:12.49 6:11.61 6:0.88	3.35 ppm	0.30 ± 0.01 0.29 ± 0.01[b]	0.74 ± 0.02 0.72 ± 0.02[b]	0.27 ± 0.01 0.26 ± 0.01[b]
1b:**2** 6:8.02 6:7.15 6:0.87	3.33 ppm	0.28 ± 0.01	0.69 ± 0.01	0.26 ± 0.01
1b:**2** 6:4.26 6:3.44 6:0.82	3.30 ppm	0.28 ± 0.01	0.64 ± 0.01	0.26 ± 0.01
1b:**2** 6:2.26 6:1.51 6:0.75	3.22 ppm	0.28 ± 0.01	0.50 ± 0.01	0.27 ± 0.01
1b:**2** 6:1.26 6:0.79 6:0.47	3.17 ppm	0.28 ± 0.01	0.43 ± 0.01	*c*
1b:**2** 6:0.66 6:0.47 6:0.19	3.16 ppm	0.27 ± 0.01	0.41 ± 0.01	*c*

[a] **1b** (5 mM) in water-saturated $CDCl_3$ solutions. [b] Values were obtained after correction for the effect of the changed viscosity of the solution. [c] Not measured because of the low signal-to-noise ratio.

is that the nonencapsulated THABr forms a complex with the monomer of **1b** that is in fast exchange, on the NMR time scale, with the complex components, while the encapsulated THABr diffuses as one molecular entity with the hexamer of **1b** and is in slow exchange with other THABr pools. The numerical values of the diffusion coefficients as a function of the **1b**/**2** ratio are tabulated in Table 1.

Interestingly, when we measured the diffusion coefficients of **1b** and water in the THABr-containing $CDCl_3$ solutions as a function of the **1b**/H_2O ratio, we found a much less dramatic effect of this ratio on the diffusion coefficients of the water peak, as compared with that previously observed for the hexamer of **1b** in the $CDCl_3$ solution in the absence of THABr.[6b] As an example, Figure 3 shows the signal decay of one of the peaks of resorcinarene **1b** and the water peak, respectively, at a **1b**/H_2O ratio of about 6:8.4 for the $CDCl_3$ solutions in the absence (a and b) and presence (c and d) of THABr. Figure 3 clearly shows that there is a large difference in the water signal decay as a function of the diffusion weighting, b, in the two $CDCl_3$ solutions (compare Figures 3b and 3d). While there is only a limited effect on the diffusion coefficient of the water peak when the **1b**/H_2O ratio is varied in the presence of THABr, there is a dramatic effect of the **1b**/H_2O ratio on the diffusion coefficient of the water peak in the absence of THABr. The extracted diffusion coefficients for the $CDCl_3$ solutions containing THABr are tabulated in Table 2, and the diffusion coefficients of the water peak and the peak of **1b** as a function of the **1b**/H_2O ratio in the presence and absence of **2** are graphed in Figure 4.

When there is a large excess of H_2O relative to **1b**, the diffusion coefficient of H_2O is similar in both the presence and the absence of THABr. In the presence of THABr, the diffusion coefficient of the water molecules is much higher than the diffusion coefficient of **1b**. Even when the ratio of **1b**/H_2O was significantly smaller than 6:8, in the presence of THABr, the diffusion coefficient of the water peak was

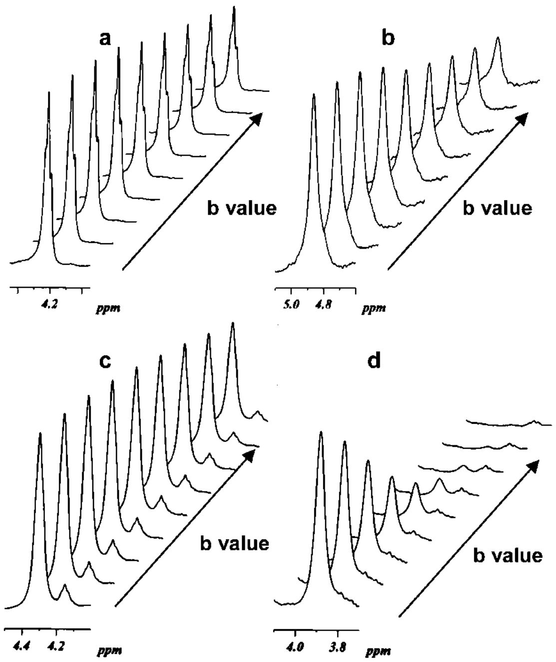

Figure 3. ^1H NMR signal decay as a function of the *b* values, where *b* is equal to $-\gamma^2\delta^2g^2(\Delta-\delta/3)$ (400 MHz, 298 K), for one of the peaks of **1b** (a and c) and for water (b and d) in $CDCl_3$ solutions when the **1b**/H_2O ratio is about 6:8.4 for solutions with (c and d) and without THABr (a and b).

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(13) NMR diffusion measurements were performed on a 400 MHz NMR spectrometer equipped with a Great 1/10 gradient system. All diffusion coefficients reported are means ± standard deviation of the mean of at least three measurements. Only data for which the correlation coefficients were higher than 0.999 were included. Because of the relatively short T_2 of the water peaks, diffusion experiments were performed using the stimulated echo diffusion sequence.[9b]

Table 2. Effect of the **1b**/H_2O Ratio on the Diffusion Coefficients of **1b** and the Water Peaks in the $CDCl_3$ Solutions in the Presence of THABr at 298 K

system[a] **1b**/water ratio	water chemical shift	diffusion coefficients [x10^5 cm^2/sec] **1b** 1.3 ppm	water	$CHCl_3$
water saturated $CDCl_3$	1.53 ppm		5.18 ± 0.08	2.52 ± 0.02
			4.15 ± 0.06[b]	2.02 ± 0.02[b]
43.9 mM dry $CDCl_3$ + H_2O	2.66 ppm	0.22 ± 0.01	3.31 ± 0.04	2.06 ± 0.05
6:24.3		0.22 ± 0.01[b]	3.25 ± 0.04[b]	2.02 ± 0.05[b]
43.9 mM dry $CDCl_3$ + H_2O	3.02 ppm	0.22 ± 0.01	2.88 ± 0.03	1.99 ± 0.03
6:16.1		0.22 ± 0.01[b]	2.92 ± 0.03[b]	2.02 ± 0.03[b]
28.7 mM $CDCl_3$	3.45 ppm	0.23 ± 0.01	2.33 ± 0.04	2.12 ± 0.02
6:12.6		0.22 ± 0.01[b]	2.22 ± 0.04[b]	2.02 ± 0.02[b]
43.9 mM dry $CDCl_3$ + H_2O	3.74 ppm	0.22 ± 0.01	2.15 ± 0.01	2.04 ± 0.03
6:10.1		0.22 ± 0.01[b]	2.13 ± 0.01[b]	2.02 ± 0.03[b]
43.9 mM dry $CDCl_3$ + H_2O	3.89 ppm	0.22 ± 0.01	2.00 ± 0.03	1.94 ± 0.07
6:8.4		0.23 ± 0.01[b]	2.08 ± 0.03[b]	2.02 ± 0.07[b]
58.4 mM $CDCl_3$	4.50 ppm	0.19 ± 0.01	1.20 ± 0.02	1.92 ± 0.03
6:4.1		0.20 ± 0.01[b]	1.26 ± 0.02[b]	2.02 ± 0.03[b]

[a] In these solutions, the **1b**:**2** ratio was 1:1. [b] Values were obtained after correction for the effect of the change in the viscosity of the solution.

still several times that of **1b**. These results are in contradiction with what we recently found for the effect of the **1b**/H_2O ratio on the diffusion coefficient of water in the absence of THABr. There we found that when there are fewer than eight water molecules per six molecules of **1b**, the diffusion coefficient of the water peak is equal to that of **1b**.[6b]

It seems that the most plausible explanation for the different behavior of the water diffusion coefficients, when the **1b**/H_2O ratio is varied for the $CDCl_3$ solutions with and without THABr, is the different role of the water molecules in both solutions. In the $CDCl_3$ solution in the absence of THABr, the water molecules seem to be part of the supramolecular structure of the capsule. Indeed, we found that there are about eight water molecules per six molecules of **1b** that have the same diffusion coefficient as **1b** in the hexamer. As previously pointed out diffusion measurements cannot distinguish between encapsulated water molecules and water molecules that are part of the hexamer since, in both situations, the water diffusion coefficient should be equal to the diffusion coefficient of the hexamer. However, because of the fast exchange of H_2O with bulk water and the fact that a [(**1a**)$_6$(H_2O)$_8$]-type capsule was observed in the solid state, we believe that the more plausible explanation is that the eight water molecules, which have the same diffusion coefficient as the hexamer, are part of the supramolecular structure of the capsule rather than encapsulated water molecules.[6b] However, in the presence of THABr, it seems that there are no water molecules that are part of the supramolecular system of the capsule. Even when we have only four water molecules per six molecules of **1b** in the presence of **2**, the diffusion coefficient of the H_2O peak is more than six times that of the hexamer, while in the absence of **2**, for all ratios of **1b**:H_2O of less than 6:8, the water diffusion coefficient was similar to the diffusion coefficient of **1b**. Therefore, it is tempting to speculate that, in the presence of THABr, there is no need for a significant number of water molecules in order to construct the supramolecular capsule. It seems that due to the cation−π interaction, the THABr acts as a pseudotemplate for the self-assembly of the **1b** units to form the hexameric capsule. Here, the assistance of the water, or the mediation of the water molecules, seems to be needed less. This is in line with the much higher affinity of THABr toward the cavity of **1b**, as compared with the affinity of the $CDCl_3$ molecules.[6a]

In conclusion, we have demonstrated that, in the formation of the hexameric capsule of **1b** in the presence of THABr, the nonencapsulated salt forms a 1:1 complex with **1b**. In addition, we showed that the role played by the water molecules in both capsules is different. It seems that, in the presence of **2**, the mediation of the water molecules is needed less and therefore they are not part of the supramolecular structure.

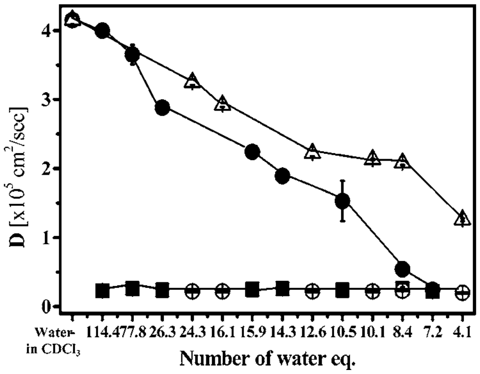

Figure 4. Diffusion coefficients (×10^5) of **1b** in the presence (○) and absence (■) of **2** and of water peaks in the presence (△) or absence (●) of **2** as a function of the water equivalents per 6 equiv of **1b**.

Supporting Information Available: Explanation of the extraction of diffusion coefficients from NMR diffusion experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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