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The Role of Water Molecules in a Resorcinarene Capsule As Probed by NMR Diffusion Measurements

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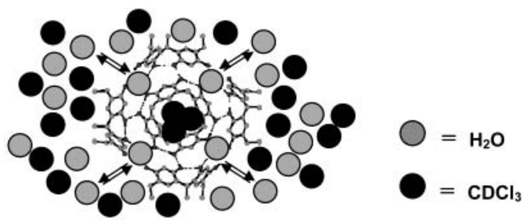
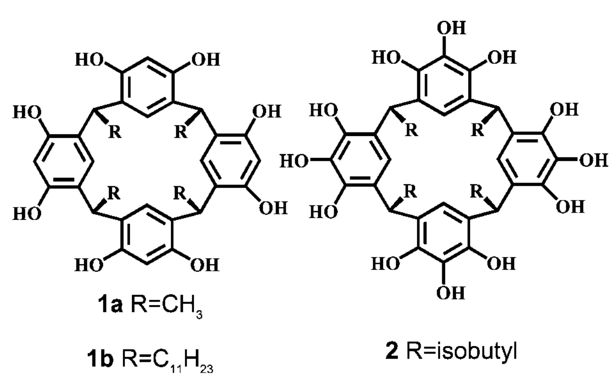
ABSTRACT



NMR diffusion measurements were used to probe the role of water molecules in a resorcinarene capsule in a $CDCl_3$ solution. It was found that the water/resorcinarene ratio affects both the chemical shift and the diffusion coefficient of the water molecules. From the NMR diffusion measurements we could conclude that the major species in the chloroform solution is the hexamer having eight water molecules that are in fast exchange, on the NMR time scale, with the bulk water.

Molecular capsules[1,2] in general and those based on hydrogen bonds in particular have attracted considerable attention in recent years.[3] Molecular capsules are now being used as artificial compartments and nanometric reaction chambers.[4] In this context, molecular capsules, having a relatively large cavity, are even more important. Recently, it was demonstrated that resorcin[4]arenes and pyrogallol[4]arenes, such as those shown in Scheme 1, form large capsules with large cavities.[5] These large molecular capsules are generally assembled from a multiplicity of molecules. In fact, it was found that resorcinarene **1a** self-assembles in the solid state to a hexameric capsule of the $(\mathbf{1a})_6(H_2O)_8$-type.[5a] It was also demonstrated that, with suitable guests, hexameric capsules

Scheme 1



(1) For a few early examples of hydrogen bond dimeric capsules see: (a) Shimuzu, 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 reviews on molecular capsules see: (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018−1033. (c) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, *Chem. Commun*. **2001**, 509−518. (d) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed*. **2002**, *41*, 1488−1508.

(3) For recent reviews concerning hydrogen bond capsules see: (a) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643. (b) Böhmer, V.; Vysotsky, M. O. *Aust. J. Chem.* **2001**, *54*, 671−677.

(4) (a) Hof, F.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4775−4777. (b) Chen, J.; Körner, S.; Craig, S. L.; Lin, S.; Rudkevich, D. M.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 2593−2596.

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can be detected in a water-saturated solution of $CDCl_3$.[6] Recently it was reported that systems such as **2** form stable hexameric capsules even in protic solution.[5c]

Very recently it was demonstrated that **1b** forms a hexameric capsule in a water-saturated solution of $CDCl_3$ without the need for an additional guest,[7] thus emphasizing the role of water molecules in these hydrogen bond capsules. In addition, it was concluded that several solvent molecules are encapsulated in such hexameric capsules.[7] These observations imply that such capsules are many-bodied molecular species in which water molecules can play a crucial role. Water molecules may be part of the capsule structure and/or be encapsulated in the capsule. Water molecules may interact with the hexameric capsule from the outside or float freely in the bulk. We therefore decided to follow the NMR diffusion characteristics of water molecules in such systems where the water/resorcinarene ratio is varied.

NMR diffusion measurements,[8] which have seldom been used by supramolecular chemists, can be used to probe complexation, aggregation, and ion pairing and may be used to study intermolecular interactions.[9] Recently we have demonstrated that this method is extremely useful in monitoring encapsulations.[10] This technique was very recently used to probe the hexameric nature of the capsule of **1b** in $CDCl_3$ solutions.[7]

Figure 1 shows sections of the ^1H NMR spectra of **1b**[11]

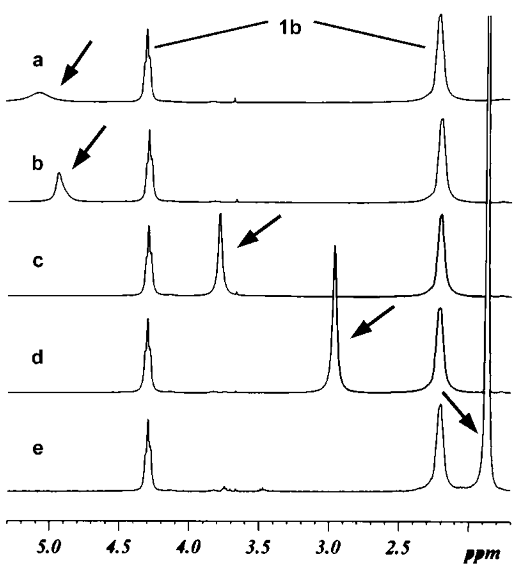

Figure 1. Sections of the ^1H NMR spectra (400 MHz, 298 K) of the $CDCl_3$ solution of **1b** for different **1b**:H_2O ratios: (a) 6:7.2, (b) 6:8.4, (c) 6:14.3, (d) 6:26.3, and (e) 6:114.4. The arrows indicate the water peaks in the solutions.

in $CDCl_3$ solutions at 298 K at different **1b**/H_2O ratios. This figure shows that this ratio affects both the line shape and chemical shift of the water peak in the $CDCl_3$ solution.[12]

Only one peak of water is observed at all **1b**:H_2O ratios, meaning that if there are different water pools they are in the fast exchange regime under our experimental conditions (400 MHz, 298 K).

Interestingly, when we measured the diffusion coefficients[13] of **1b** and water in those $CDCl_3$ solutions we found a dramatic effect of the **1b**/H_2O ratio on the diffusion coefficients of the water peak. As an example, Figure 2

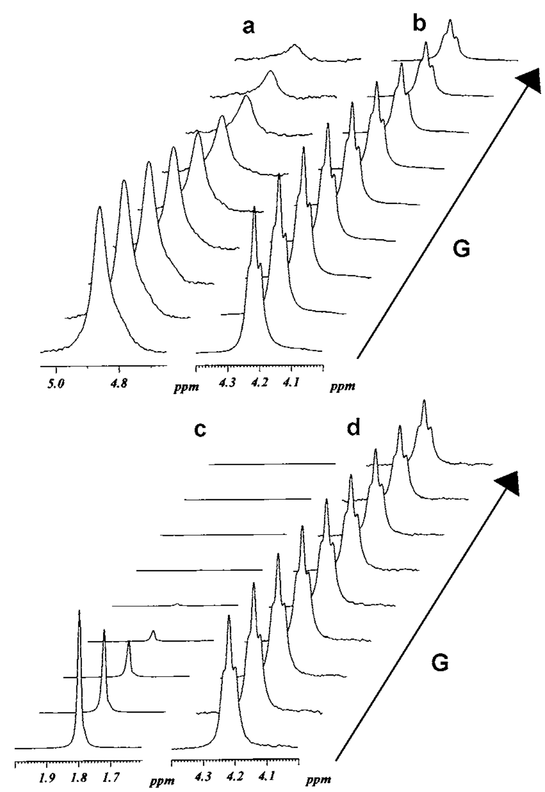

Figure 2. ^1H NMR signal decay as a function of the gradient strength (G) (400 MHz, 298 K) of water (a and c) and of one of the peaks of **1b** in $CDCl_3$ solutions when the **1b**/H_2O ratios were 6:8.4 (a and b) and 6:114.4 (c and d).

shows the signal decay of one of the peaks of resorcinarene **1b** and the water peak at two different **1b**/H_2O ratios. This figure clearly shows that, although there is only a small effect

(5) (a) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469−471. (b) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4837−4841. (c) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Chem. Commun.* **2001**, 2376−2377.

(6) (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. (c) Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2001**, 2374−2375.

(7) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, in press.

(8) (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 to chemical systems see: Stilbs, P. *Prog. NMR Spectrosc.* **1987**, *19*, 1−45.

(9) For a few selected examples see: (a) Rymdén, R.; Carlfors, J.; Stilbs, P. *J. Incl. Phenom.* **1983**, *1*, 159. (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*, 2639−2644.

on the signal decay as a function of the gradient strength, *G*, and hence on the diffusion coefficient of **1b** there is a dramatic effect on the diffusion coefficient of the water peak when the **1b**/H_2O ratio is varied.

The extracted diffusion coefficients are tabulated in Table 1 and the diffusion coefficients of the water peak and the peak of **1b** as a function of the **1b**/H_2O ratio are graphed in Figure 3.

Table 1. The Effect of the **1b**/H_2O Ratio on the Diffusion Coefficients of **1b**, Water, and the Water Chemical Shift at 298 K

system **1b**:water ratio	water chemical shift, ppm	diffusion coefficients [$\times 10^5$ cm^2/s]		
		1b 1.3 ppm	water	$CHCl_3$
water-satd $CDCl_3$ [a]	1.53		5.18 ± 0.08	2.52 ± 0.02
			4.15 ± 0.06[b]	2.02 ± 0.02[b]
1b/3.1 mM water-satd $CDCl_3$ 6:114.4	1.87	0.27 ± 0.01	4.67 ± 0.07	2.36 ± 0.01
		0.23 ± 0.01[b]	4.00 ± 0.06[b]	2.02 ± 0.01[b]
1b/5.6 mM water-satd $CDCl_3$ 6:77.8	2.02	0.30 ± 0.01	4.28 ± 0.16	2.37 ± 0.03
		0.26 ± 0.01[b]	3.65 ± 0.14[b]	2.02 ± 0.03[b]
1b/32.0 mM water-satd $CDCl_3$ 6:26.3	2.96	0.23 ± 0.01	2.75 ± 0.02	1.93 ± 0.02
		0.24 ± 0.01[b]	2.88 ± 0.02[b]	2.02 ± 0.02[b]
1b/32.0 mM $CDCl_3$ 6:15.9	3.59	0.23 ± 0.01	2.05 ± 0.02	1.85 ± 0.03
		0.25 ± 0.01[b]	2.24 ± 0.02[b]	2.02 ± 0.03[b]
1b/26.7 mM water-satd $CDCl_3$ 6:14.3	3.78	0.24 ± 0.01	1.74 ± 0.02	1.86 ± 0.11
		0.26 ± 0.01[b]	1.89 ± 0.02[b]	2.02 ± 0.12[b]
1b/31.6 mM dry $CDCl_3$ 6:10.5	3.55	0.24 ± 0.01	1.55 ± 0.29	2.04 ± 0.01
		0.24 ± 0.01[b]	1.53 ± 0.29[b]	2.02 ± 0.01[b]
1b/27.4 mM $CDCl_3$ 6:8.4	4.94	0.26 ± 0.01	0.54 ± 0.01	2.02 ± 0.01
1b/30.6 mM dry $CDCl_3$ 6:7.2	5.06	0.21 ± 0.01	0.22 ± 0.03[c]	1.89 ± 0.05
		0.22 ± 0.01[b]	0.24 ± 0.03[b,c]	2.02 ± 0.05[b]

[a] The water concentration in this solution was estimated to be about 50 mM, based on integration of the ^1H NMR spectrum. [b] Values obtained after correction for the change in the viscosity of the solution. [c] The correlation coefficients were higher than 0.992 as compared with more than 0.999 for all other measurements.

The diffusion data clearly show that, although the **1b**/H_2O ratio has some effect on the viscosity of the sample and hence on the diffusion coefficients of the different species in the solution, there are much more dramatic changes in the diffusion coefficients of the water peak. The change in the viscosity of the sample is manifested by the changes in the observed diffusion coefficient of the $CDCl_3$. The most important observations are the facts that when there are less than eight water molecules per six molecules of **1b** the diffusion coefficient of the water peak is equal to that of **1b**. However, when there are more than eight water molecules per six molecules of **1b** the observed diffusion coefficients of the water peak are much larger than that of **1b**. For example, when the **1b**/H_2O ratio was 6 to 8.4 the diffusion coefficient of the water peak was already nearly twice that of the resorcinarene **1b**. This implies that the water molecules, beyond the eight molecules needed for the assembly of the molecular capsule, experience much faster diffusion as expected from bulk water in $CDCl_3$.

In principle, in the slow exchange regime, both water molecules that form part of the capsule skeleton or encapsulated water molecules should have the same diffusion coefficient as the resorcinarene moieties in the capsule. However, water molecules, interacting weakly with the surface of the resorcinarene moieties, and bulk water should have much higher diffusion coefficients than that of **1b**. Since we observe only one peak for the water molecules at all **1b**/H_2O ratios, it is clear that the measured diffusion coefficient should be a weighted average of the diffusion coefficients of the different water pools in the solution. When the solution contains an excess of water beyond the 6 to 8 ratio of **1b** to H_2O, the additional water molecules experience a much faster diffusion coefficient and, hence, the weighted average diffusion coefficient measured for the water increases dramatically. It is interesting that such an increase is observed when the **1b**/H_2O ratio is larger than the 6:8 stoichiometry found for the molecular capsule of **1a** in the solid state.[5a] Although diffusion measurements cannot distinguish between water molecules that are part of the capsule skeleton and those encapsulated in it, it seems that the most plausible explanation for the above observations is that the hexameric capsule of the $(\mathbf{1b})_6(H_2O)_8$-type is the major species in the solution as found in the solid state. Such a hexameric capsule was suggested for the benzene solution of **1b**.[5a] In the presence of an excess of water in the solution, the protons

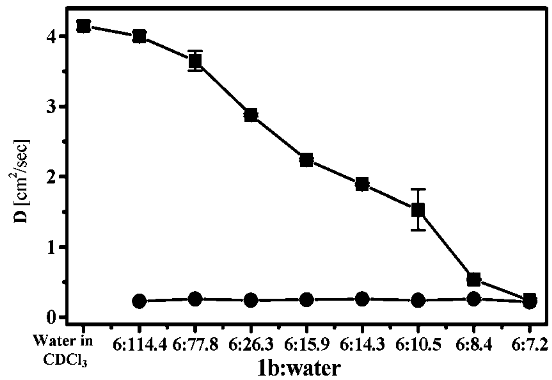

Figure 3. Diffusion coefficients ($\times 10^5$) of **1b** (●) and water (■) as a function of the **1b**/H_2O ratio.

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

(12) The line shape and the chemical shift of the H_2O peaks in the ^1H NMR spectra were found to be very sensitive to the origin of the $CDCl_3$ used. For more details see the Supporting Information.

(13) The NMR diffusion measurements were performed on a 400-MHz Avance Bruker NMR spectrometer equipped with a Great1/10 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 (see ref 8b).

of the water molecules in the capsule and the proton of the freely tumbling water molecules are in fast exchange. We found no evidence for a significant water population beyond the eight water molecules per six molecules of **1b** which might, for example, be encapsulated in the large cavity of this capsule which apparently is only partially occupied by the solvent molecules.

In summery, our observations are in line with the fact that a hexamer of the $(\mathbf{1b})_6(H_2O)_8$-type is the major species in the water-saturated solution of $CDCl_3$. No evidence was found for a large fraction of encapsulated water molecules. In addition, we have demonstrated that NMR diffusion measurements can assist in determining the nature of the capsule that prevails in solution and that one can use this method to probe the role of water molecules in such hydrogen bond supramolecular capsules.

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Supporting Information Available: Sections of the ^1H NMR spectra showing the behavior of the water peak in different solutions of **1b** at different **1b**:water ratios in $CDCl_3$ solution of different sources. This material is available free of charge via the Internet at http://pubs.acs.org.

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