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COMMUNICATIONS

Published on Web 11/26/2002

# Spontaneous Formation of Hexameric Resorcinarene Capsule in Chloroform Solution as Detected by Diffusion NMR

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Received June 12, 2002

In recent years, molecular capsules of different kinds were prepared.[1] Among those capsules, molecular capsules held together by hydrogen bonds attracted much attention.[2,3] Substituted calixarenes, [2−4] and more recently resorcinarenes,[5] were shown to form such molecular capsules. The recent interest in resorcinarene capsule stems from the pioneering work of MacGillivray and Atwood who demonstrated that resorcinarene (**1a**, Chart 1) forms a large capsule consisting of six **1a** units and eight water molecules (i.e., [(**1a**)$_6$($H_2O$)$_8$]) in the solid state and suggested its possible role for molecular recognition in solution.[6] Very recently Shivanyuk and Rebek demonstrated that under certain experimental conditions, that is, water-saturated $CDCl_3$ as solvent and a suitable guest such as tetrahexylammonium bromide (THABr, **2a**) or $Bu_4SbBr$, **1b** (Chart 1) forms a stable hexameric molecular capsule in solution.[5a,b]

The pulse gradient spin−echo (PGSE) technique is a powerful NMR method for measuring molecular diffusion.[7] In recent years NMR diffusion measurements were used to probe complexation of different complexes,[8a,b] to study ion-pairing aggregation[8c] and the structure of organometallic compounds,[8d] and to probe rotaxane formation.[8e] Recently, we were able to show that NMR diffusion is a powerful tool for probing encapsulation.[9a,b] We therefore thought to use this technique to probe the structure of **1b** in $CDCl_3$ solutions. Here, we report that NMR diffusion measurements show unequivocally that, surprisingly, **1b**, assembles into a hexameric capsule in chloroform spontaneously without the aid of any guest by encapsulating several chloroform molecules, which seems to occupy different chemical environments on the NMR time scale.

Compound **1b** was prepared according to the literature[10] and afforded the expected spectrum as shown in Figure 1A. Indeed, addition of **2a** to the water-saturated $CDCl_3$ solution of **1b** gave the spectrum shown in Figure 1B which is identical to that reported previously for the hexameric capsule of **1b**.[5a]

Interestingly, when we measured the diffusion coefficients for the two species shown in Figure 1, A and B, we found the same diffusion coefficient[11] ($0.28 \pm 0.02 \times 10^{-5}$ cm$^2$ s$^{-1}$) for both molecular species which is inconsistent with the assignment of these spectra to the monomer and the hexameric capsule of **1b**, respectively. This assignment is not probable since it is reasonable to assume that the very large difference in the molecular weight of the monomeric and the hexameric forms of **1b** (molecular weights of 1104 g/mol vs 6624 g/mol) should be reflected in their diffusion coefficients. However, the diffusion coefficients of the peaks of **1b**, in water-saturated $CDCl_3$ and in commercial $CDCl_3$ before and after addition of **2a**, were found to be the same within experimental errors (Table 1).

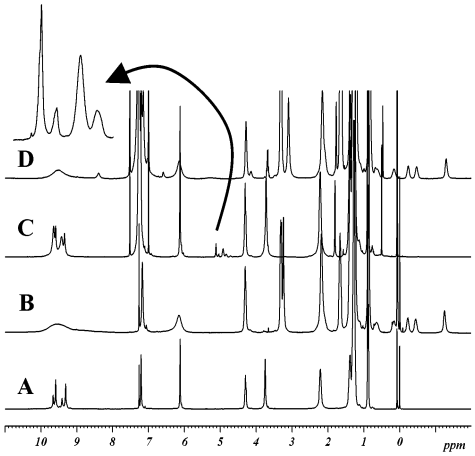
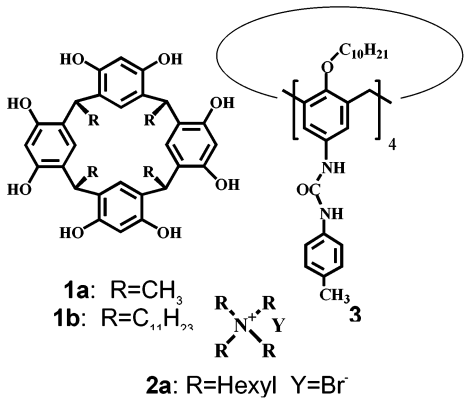



***Figure 1.*** $^1$H NMR spectra (400 MHz, 298 °K) in a water-saturated solution of (A) **1b** in $CDCl_3$, (B) **1b** and **2a** in $CDCl_3$, (C) **1b** in $CHCl_3$, (D) same as (C) after addition of **2a**. The inset shows the peaks attributed to the encapsulated chloroform molecules observed when **1b** is dissolved in $CHCl_3$.

***Chart 1***




Taking into account the previous assignment of Shivanyuk and Rebek[5a] and the low diffusion coefficients measured in the $CDCl_3$ solution, we began to suspect that the spectrum of **1b** shown in Figure 1A in $CDCl_3$ represents mostly a hexameric capsule. It should be noted that the diffusion coefficient of **1b** is significantly lower than that of the dimeric capsule of the teraureacalix[4]arene derivative (**3**) having a molecular weight of 3152 g/mol, which was found to be $0.40 \pm 0.01 \times 10^{-5}$ cm$^2$ s$^{-1}$ ($CDCl_3$, 5 mM, 298 K).[9c] To further challenge this result the following experiments were performed: First **1b** was dissolved in $CHCl_3$, and indeed the same spectrum was obtained with additional singlets (298 K, 400 MHz), which were found in the range of 4.8−5.1 ppm.[12] These peaks, which are 2.1−2.4 ppm upfield compared with the "free" $CHCl_3$, were attributed to the encapsulated chloroform molecules (see

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10.1021/ja0272686 CCC: $22.00 

***Table 1.*** Diffusion Coefficients ($\times 10^5$ in $cm^2\ s^{-1}$) of **1b** (3 mM) and **2a** in Different Mixtures of Water-Saturated $CDCl_3$ at 298 K

| system[a] | 1.3 ppm **1b** | 4.2 ppm **1b** | free **2a** | $CHCl_3$ |
|---|---|---|---|---|
| **1b** | 0.27±0.01 | 0.26±0.01 | | 2.36±0.01 |
| **1b:2a** | 0.31±0.02 | 0.29±0.02 | 0.74±0.02 | 2.45±0.04 |
| **1b:2a** +50 equiv DMSO-$d_6$ | 0.30±0.01 | 0.29±0.01 | 0.71±0.01 | 2.27±0.05 |
| | 0.33±0.01[b] | 0.31±0.01[b] | 0.77±0.01[b] | 2.45±0.06[b] |
| **1b:2a** + 200 equiv DMSO-$d_6$ | 0.38±0.01 | 0.36±0.02 | 0.67±0.01 | 2.22±0.01 |
| | 0.42±0.01[b] | 0.40±0.01[b] | 0.74±0.01[b] | 2.45±0.02[b] |
| **1b:2a** + 560 equiv DMSO-$d_6$ | 0.38±0.01 | 0.36±0.01 | 0.61±0.01 | 2.12±0.03 |
| | 0.44±0.01[b] | 0.42±0.01[b] | 0.71±0.01[b] | 2.45±0.04[b] |
| **1b:2a** + 500 equiv $CD_3CN$ | 0.25±0.01 | 0.23±0.02 | 0.70±0.01 | 2.43±0.04 |
| **1b:2a** + 1500 equiv $CD_3CN$ | 0.42±0.01 | 0.44±0.02 | 0.72±0.02 | 2.41±0.05 |
| **1b:2a** + 2500 equiv $CD_3CN$ | 0.48±0.01 | 0.47±0.01 | 0.76±0.01 | 2.37±0.08 |
| | 0.50±0.01[b] | 0.48±0.01[b] | 0.79±0.01[b] | 2.44±0.08[b] |

[a] The ratio between **1b** and **2a** was 1:1. [b] Values obtained after correction for the effect of increased viscosity of the solution caused by the addition of DMSO-$d_6$.

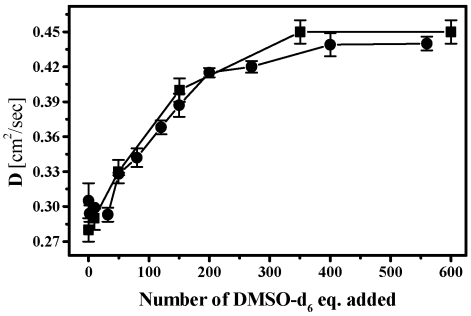


***Figure 2.*** Changes in the diffusion coefficients ($\times 10^5$ in $cm^2\ s^{-1}$) for the water-saturated $CDCl_3$ solution of **1b** (■) and **1b** in the presence of **2a** (●) as a function of the addition of DMSO-$d_6$.

Figure 1C). These new peaks were found to have the same diffusion coefficient as that of **1b** within experimental errors in different concentrations. Indeed, according to integration we could conclude that several molecules of $CHCl_3$ are needed to fill the cavity of the hexameric capsule. When **1b** was dissolved in 50% $CHCl_3$ and 50% $CDCl_3$ we found the same new singlets, but their overall intensity was half that of the previous case. These singlets suggest that the encapsulated solvent molecules occupy several distinguishable positions, on the NMR time scale in the capsule at this temperature (see inset in Figure 1). When **2a** is added to this solution, the peaks of the encapsulated chloroform molecules disappear (Figure 1D), and the spectrum of the hexameric capsule encapsulating **2a** is regenerated (compare Figure 1, B and D). This is to be expected since it is reasonable to assume that tetrahexylammonium bromide has a higher affinity toward the cavity of the hexameric capsule than chloroform molecules. Such higher affinity of charged guests toward the inner cavity of the hydrogen-bound capsule was previously reported.[9b,13] In addition, we titrated both the solution shown in Figure 1, A and B, with DMSO-$d_6$, a solvent which disrupts hydrogen bonds which seems to be the driving force for the formation of the above hexameric capsule. As a result of these titrations, although an increase in the viscosity was observed, an increase in the diffusion coefficient of the peaks of **1b** was found as depicted in Figure 2.

The diffusion coefficient of the resorcinarene in the hexameric capsule (**1b**)$_6$**2a** increased from $0.30 \pm 0.02 \times 10^{-5}$ $cm^2\ s^{-1}$ to $0.43 \pm 0.01 \times 10^{-5}$ $cm^2\ s^{-1}$ upon addition 560 equiv of DMSO-$d_6$ (relative to **1b**) and $0.49 \pm 0.01 \times 10^{-5}$ $cm^2\ s^{-1}$ upon addition of 2500 equiv of $CD_3CN$ (Table 1 and Figure 2). After addition of 40 or 500 equiv of DMSO-$d_6$ or $CD_3CN$, respectively, there is no indication of the encapsulated guests. However, the diffusion coefficient reached a plateau only after the addition of 400 or 2500 equiv of DMSO-$d_6$ or $CD_3CN$, respectively. The same phenomenon was observed for the solution of **1b** in the absence of the tetrahexylammonium bromide where we found that the same amount of DMSO-$d_6$ was needed to get to the plateau value of the diffusion coefficient (Figure 2). After addition of excess $CD_3CN$ or DMSO-$d_6$ very similar $^1H$ NMR spectra were obtained (data not shown) that are very different from that shown in Figure 1, A and B. All these observations are consistent with the fact that a hexameric capsule exists even in the absence of any guest. In fact, it seems that the chloroform molecules are enough to induce the formation of the hexameric capsule and that the stability of the capsules are similar, although the affinity of **2a** toward the cavity of the hexamer is higher than that of the chloroform molecules.

In conclusion, we have demonstrated, with the aid of diffusion NMR, that resorcinarene **1b** self-assembles spontaneously into a hexameric capsule in chloroform. These results demonstrate that **1b** contains enough molecular information to allow the formation of its hexamer in $CDCl_3$ in which several chloroform molecules are encapsulated.

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JA0272686