Octahydroxypyrindine[4]arene Self-Assembles Spontaneously To Form Hexameric Capsules and Dimeric Aggregates

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Abstract: In recent years it has been observed that resorcin[4]arenes and pyrogallol[4]arenes form hydrogen-bonded hexameric capsules in nonpolar solvents. In the present study we have used NMR spectroscopy, with an emphasis on diffusion NMR, to investigate the self-assembly and the aggregation mode of solutions of octahydroxypyrindine[4]arene (1b) in chloroform. In spectroscopic studies, the hexameric capsule of C-undecylresorcin[4]arene (2b) was used as a reference compound and in some cases also as an internal reference. The current diffusion NMR spectroscopy study shows, in contrast to a previous report, that compound 1b self-assembles spontaneously into hexameric and dimeric aggregates in solutions in chloroform. The $^1$H NMR and diffusion NMR spectroscopic studies on a solution of 1b in CHCl$_3$ show the presence of new upfield-shifted peaks, which diffuse with the same diffusion coefficient as the hexameric peaks in the spectrum.

Keywords: hexameric capsules · hydrogen bonds · NMR spectroscopy · self-assembly · supramolecular chemistry

Introduction

Over the last decade hydrogen-bonded molecular capsules have attracted much interest.[1,2] First, dimeric capsules based on tetraureacalix[4]arenes were characterized.[3] Then, hydrogen-bonded hexameric capsules based on resorcin[4]arenes and pyrogallol[4]arenes became the focus of attention.[4,5] In 1997, a seminal paper in this field by MacGillivray and Atwood reported the spectacular solid-state structure of the hexameric capsule of C-methylresorcin[4]arene (2a, Scheme 1).[4a] In 1999, Mattay and co-workers reported the solid-state structure of the hexameric capsule of C-isobutylpyrogallol[4]arene (3a, Scheme 1).[5a] In 2001, Shivanyuk and Rebek demonstrated that C-undecylresorcin[4]arene (2b) forms hexameric capsules in a water-saturated chloroform solution in the presence of suitable guest molecules, such as tetrahexylammonium bromide and tetrabutylantimony(V) bromide.[5b,7] Therefore, it was assumed that guest molecules are required to induce the formation of such hexameric capsules in solution. By using diffusion NMR spectroscopy, we later demonstrated that molecules such as resorcin[4]arene and pyrogallol[4]arene self-assemble spontaneously to form hexameric capsules in solution in chloroform, and in other organic solvents, without the addition of a specific guest molecule.[6,9] With diffusion NMR spectroscopy, we demonstrated that resorcin[4]arenes 2b and 2c self-assemble into hexameric capsules with eight water molecules, that is, [2b$_6$(H$_2$O)$_8$] and [2c$_6$(H$_2$O)$_8$], whereas pyrogallol[4]arenes 3a and 3b form 3a$_6$- or 3b$_6$-type capsules (Scheme 1).[6a,c,d] Furthermore, several complexes of resorcin[4]arene 2b, which were prepared by Aoyama and co-workers during the 1990s and showed 1:1

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Figure S1 shows the diffusion-ordered spectroscopy (DOSY) of a 1:1 mixture of 1b/2b (20:20 m/s) in CDCl$_3$. Figure S2 shows the $^1$H NMR spectra of 1b (20 m/s) in CHCl$_3$, in the absence and in the presence of TFA (1, 2, and 3 mL). Table S1 is a summary of the diffusion coefficients of 1b (20 m/s) and 2b (20 m/s) and a 1:1 mixture of 1a/2b in the presence and in the absence of TFA (1 or 3 mL) in CDCl$_3$, and a sample of 1b (20 m/s) in CHCl$_3$.

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Results and Discussion

C-Tetra-n-undecyl-2,6,8,12,14,-18,20,24-octahydroxyppyridine[4]arene (1b, Scheme 1) was synthesized according to the procedure described in the literature.[12] The 1H NMR spectrum of 1b in CDCl3 afforded the same spectrum as that reported earlier by Mattay and co-workers.[13] The 1H NMR spectrum of a solution of 1b (20 mM) in CDCl3 revealed the two sets of peaks that were previously assigned to the monomer and the dimer of 1b.[13] Sections of the 1H NMR spectrum of 1b are shown in Figure 1b. Diffusion NMR measurements on this sample showed that these two sets of peaks do, indeed, differ in their diffusion coefficients. However, the set of peaks previously assigned to

1b was found to have a diffusion coefficient ((0.236 ± 0.001) × 10−5) cm²s⁻¹, 20 mM, CDCl3) that is very close to that of the hexamic capsules of 2b and 3b,[8–9] which are compounds whose molecular weights are very similar to that of 1b. The set of peaks previously assigned to the monomer of 1b was found to have a higher diffusion coefficient ((0.350 ± 0.008) × 10−5) cm²s⁻¹, 20 mM, CDCl3). However, this value is lower than that expected for a monomer of 1b in this solvent system, as was shown for compound 2b.[8] Based on these diffusion results we suspected that the previously assigned dimer of 1b is in fact a hexamic aggregate and most likely, a hexamic capsule, as in the cases of compounds 2b, 2c, 3a, and 3b.[8–9] Moreover, the diffusion NMR results seem to indicate that the peaks previ-
ously assigned to the monomer of 1b are in fact those of the dimer of 1b.

To further verify the nature of the species that prevail in a solution of 1b in chloroform, the following experiments were performed: First, 2b (20 mM) was added to a sample of 1b (20 mM) for use as an internal reference for the hexameric species (Figure 1c). The rationale behind this experiment was that if 1b does indeed aggregate to form a hexamer, then both of the hexamers (i.e., those of 1b and 2b) should be very similar in size and shape, and therefore, should have very similar diffusion coefficients under the same experimental conditions (solvent, concentration, and temperature). Sections of the 1H NMR spectra of 1b (20 mM), 2b (20 mM), and a solution that contained a 1:1 mixture of 1b/2b (20:20 mM) in the presence and absence of trifluoroacetic acid (TFA; 3 µL, 135 mM) are shown in Figure 1.

The spectrum of the 1:1 mixture of 1b/2b (Figure 1c) is a superposition of the spectra of 2b (Figure 1a) and 1b (Figure 1b). The addition of TFA (3 µL, 135 mM) had no effect on the spectrum of 2b, however, it affected the spectrum of 1b and the two sets of peaks were transformed into a single set of peaks with slightly different chemical shifts. Diffusion measurements performed on the 1:1 mixture of 1b/2b (20 mM) revealed three diffusion coefficients for the three peak systems that were observed.

Figure 2 shows the signal decay of one representative peak of 2b and representative peaks of the two peak systems of 1b in the 1:1 mixture of 1b/2b (20:20 mM). Interestingly, we found that the diffusion coefficient of the slower-diffusing set of peaks of 1b ((0.237 ± 0.004) × 10⁻⁵ cm²s⁻¹ (20 mM) was similar to that of 2b ((0.234 ± 0.001) × 10⁻⁵ cm²s⁻¹ (20 mM), which is known to be a hexamer when dissolved in CDCl₃ (see also Figure 3 and Figure S1 of the Supporting Information). This data further corroborated the assumption that the slow-diffusing set of peaks of 1b actually represents a hexameric assembly of 1b rather than a dimeric species. Interestingly, the addition of TFA (3 µL, 135 mM) to the sample that contained a 1:1 mixture of 1b/2b (20 mM) gave rise to a new set of peaks for 1b (see Figure 1d) with no observed changes in the chemical shifts of 2b. As for the diffusion coefficients, the addition of TFA (3 µL, 135 mM) to the sample resulted in a much higher diffusion coefficient for the new set of peaks of 1b ((0.431 ± 0.007) × 10⁻³ cm²s⁻¹, 20 mM, CDCl₃). This value is even higher than that obtained for the fast-diffusing set of peaks of 1b prior to the addition of TFA. However, TFA had no significant effect on the diffusion coefficient of the 2b, which was ((0.242 ± 0.001) × 10⁻³ cm²s⁻¹ (20 mM, CDCl₃; see Figures 2 and 3). This result led us to believe that the addition of TFA (3 µL, 135 mM) breaks the hexameric and dimeric aggregates of 1b into monomers, thus substantiating the assumption that the solution of 1b in chloroform is actually a mixture of dimeric and hexameric aggregates.

In the diffusion measurements on a sample of 2b (20 mM) in CDCl₃ with TFA (3 µL, 135 mM), we found a slight rise in the diffusion coefficient of the hexameric capsule from ((0.239 ± 0.002) × 10⁻³) in the absence of TFA to ((0.247 ± 0.001) × 10⁻³) cm²s⁻¹ in the presence of TFA (see Figure 3). Therefore, we separately measured the diffusion coefficients of samples of 1b (20 mM) and 2b (20 mM) in CDCl₃ both before and after the addition of TFA (1 µL, 45 mM, or 3 µL, 135 mM). The diffusion coefficients obtained for all of the systems measured are presented graphically in Figure 3. (The numerical values are presented in Table S1 in the Supporting Information.) All of this data clearly demonstrates that the spectrum of 1b consists of hexameric and dimeric aggregates that are disrupted upon the addition of TFA (3 µL, 135 mM), but does not necessarily imply that these aggregates are capsular in nature.

To establish whether or not the hexameric aggregates of 1b were actually hexameric capsules, we investigated the 1H NMR spectrum of 1b in CHCl₃. In protonated media in the presence of such capsules, one would expect to find en-
capsulated solvent peaks that are shifted upfield relative to the bulk solvent peak. These peaks originate from a slow exchange on the NMR timescale between the encapsulated and bulk CHCl₃ molecules. For the resorcin[4]arene[8,9e] and pyrogallo[4]arene[8c] capsules, these new peaks appear between δ = 4.7 and 5.2 ppm. A comparison of the ¹H NMR spectra of 1b (20 mM) in CDCl₃ (Figure 4a) and in CHCl₃ (Figure 4b) shows two new additional peaks at δ = 6.37–6.39 and 6.53–6.55 ppm, which were attributed to the encapsulated chloroform molecules. The diffusion coefficient of 1b (30 mM) in CHCl₃ was ((0.252 ± 0.006) × 10⁻⁵) cm² s⁻¹ and the diffusion coefficients of these two new peaks were ((0.248 ± 0.003) × 10⁻⁵) and ((0.249 ± 0.002) × 10⁻⁵) cm² s⁻¹, respectively. These findings prove that the hexameric aggregates formed when 1b is dissolved in chloroform are in fact hexameric capsules. These results imply that 1b shows similar behavior to that of compounds 2b, 3a, and 3b in solution in chloroform.[8,9,11]

We also recorded the ¹H NMR spectrum and the diffusion coefficients of the 1:1 mixture of the two compounds (i.e., 1b and 2b) in CHCl₃ (Figure 4d). Figure 4c shows the ¹H NMR spectrum of 2b in CHCl₃; this shows that the NMR spectrum of the 1:1 mixture of 1b/2b in Figure 4d is the superposition of the two ¹H NMR spectra of 1b and 2b in CHCl₃ (Figure 4b and c, respectively). There were no traces of new encapsulated solvent peaks and no evidence of any formation of heterohexamers of compounds 1b and 2b was obtained. This result implies that the self assembly of 1b and 2b proceeds with complete self-sorting and no heterohexamers are formed. These results are similar to earlier findings that no heterohexamers were formed in the mixtures of 2b with 3b or 2e with 3a[8b] Moreover, integration of the new peaks showed that about six to seven molecules of CHCl₃ are encapsulated in each hexameric capsule.

Interestingly, the addition of TFA (3 μL) to 1b (20 mM) in CHCl₃ resulted in the disappearance of the peaks between δ = 6.37 and 6.55 ppm that were assigned to the encapsulated CHCl₃ molecules (see Figure S2 in the Supporting Information).

The formation of hexameric and dimeric aggregates was further supported by analyzing the ¹³C NMR spectra obtained. We found that at higher concentrations the hexameric fraction increases, as expected, and that a sample of 1b (100 mM) in chloroform mainly contains the hexameric species of 1b. Figure 5a and b shows the aromatic section of the ¹³C NMR spectra of 2b and 1b, respectively, whereas Figure 5c shows the aromatic region for a 1:1 mixture of 1b/2b (20:20 mM) in chloroform. Figure 5c shows that the aromatic spectra of the hexameric capsules of 1b and 2b consist of five and six carbon peaks, respectively, and that the dimer of 1b consists of three carbon peaks. The addition of TFA (1 μL, 45 mM) to the mixture (Figure 5d) changed the ratio of hexamer to dimer in the mixture to ≈ 1:1 and left 2b unaffected. Further addition of TFA (up to a total of 3 μL) to the mixture of 1b/2b (Figure 5e) resulted in the disassembly of the hexamers and dimers of 1b to monomers and left the hexamers of 2b unaltered. Figure 5 shows that for the hexameric capsule of 1b, as with that of 2b, all carbons in the aromatic ring are chemically nonequivalent, which implies that the hexamers have a reduced symmetry. The dimer of 1b has only three carbon peaks, as does the monomer of 1b.

In conclusion, we have demonstrated that in contrast to a recent report, a solution of 1b in chloroform self-assembles spontaneously to form hexameric and dimeric aggregates.

Figure 4. ¹H NMR spectra at 298 K of a) 1b (20 mM) in CDCl₃, b) 1b (20 mM) in CHCl₃, c) 2b (20 mM) in CHCl₃, and d) a 1:1 mixture of 1b/2b (20:20 mM) in CHCl₃. The encapsulated chloroform peaks of 1b are located between δ = 6.37 and 6.55 ppm and are marked with ▼, and the encapsulated chloroform peaks of 2b are located between δ = 4.82 and 5.15 ppm and are marked with asterisks (*).

Figure 5. The aromatic sections of the ¹³C NMR spectra of solutions in CDCl₃ at 298 K for a) 2b (70 mM), b) 1b (100 mM), c) a 1:1 mixture of 1b/2b (20:20 mM) in the absence and in the presence of TFA (1 μL (d) and 3 μL (e)). Peaks of the hexamer of 2b are in purple, peaks of the hexamer of 1b are in green, peaks of the dimer of 1b are in red, and peaks of the monomer of 1b are in blue. The peaks marked with asterisks (*) are the two carbons of TFA in the sample.

Conclusion

In conclusion, we have demonstrated that in contrast to a recent report, a solution of 1b in chloroform self-assembles spontaneously to form hexameric and dimeric aggregates.
that are in thermal equilibrium. The hexameric aggregate is the major species in the 5 to 100 mM concentration range. The hexameric aggregates are molecular capsules under these conditions. In addition, the hexameric capsules of 1b and 2b do not form heterohexamers and six to seven equivalents of TFA disrupt the hexamers and dimers of 1b, but leave the 2b hexamers intact. This behavior matches previous findings for resorcin[4]arenes and pyrogallol[4]arenes in solution in chloroform and demonstrates the added value of using diffusion NMR when studying noncovalent supramolecular systems in solution.

Experimental Section

Materials: All starting materials, guest molecules, reagents, and the deuterated solvent CDC$_3$ were purchased from Aldrich (Milwaukee, WI) and used as supplied. C-Tetra-undecyl-2,6,8,12,14,18,20,24-octahydroxy-pyridine[4]arene 1b was prepared as previously described.[2]

Sample preparation: The samples in CDC$_3$ and CHCl$_3$ were prepared by dissolving 1b in the appropriate solvent up to a total volume of 0.3 mL. The titration of the various samples with TFA (1 and 3 μL) was done by adding 10 or 30 μL from a 1:10 diluted sample of TFA in CDC$_3$ to the NMR tube.

NMR methods: NMR diffusion measurements were performed by using a 400 MHz Avance Bruker NMR spectrometer equipped with a “Great 1” gradient system capable of producing magnetic field pulse gradients in the z-direction of about 50 G cm$^{-1}$. All experiments were carried out by using a 5 mm inverse probe. All diffusion measurements were performed in a 4 mm NMR tube that was inserted into a 5 mm NMR tube, which acts as a thermal insulating system and increases the accuracy and reproducibility of the diffusion measurements by reducing the chance of convection in the sample. This precaution is more important when diffusion NMR experiments are performed on nonviscous solvents with low boiling points and heat capacities. The measurements were all performed at 298 K. Diffusion measurements were performed by using an LED sequence with sine-shaped pulse gradients.[3]

$^1$H NMR diffusion measurements were performed at least three times and the reported diffusion coefficients are the mean ± the standard deviation of at least three experiments. Only data in which the correlation coefficients of Im($	ext{H}^2$) versus $\gamma_0^2G^2(t/2)^2(A-\Delta)/4$ (in which $\gamma$ is the gyromagnetic ratio, $G$ is the pulsed gradient strength, and $A$ and $\Delta$ are the time separation between the pulsed gradients and their duration, respectively) which are generally termed the “diffusion weighting” and are denoted as the $b$ values, were higher than 0.999 were reported.

The diffusion experiments were performed by using the LED pulse sequence with the following parameters: for the $^1$H NMR diffusion measurements the sine-shape pulsed gradients (4 ms in duration) were incremented from 0 to 36 G cm$^{-1}$ in 10 or 20 steps, and the pulse gradient separations ($\Delta$) were either 30 or 60 ms. For a $b$ value of 30 ms, the echo time, the mixing time, and eddy current delay were 20, 50, and 30 ms, respectively. For a $b$ value of 60 ms, the echo time, the mixing time, and eddy current delay were 20, 50, and 30 ms, respectively.