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A pulsed gradient spin echo NMR study of guest encapsulation by hydrogen-bonded tetraurea calix[4]arene dimers

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Diffusion coefficients, as obtained by the PGSE NMR technique, were used to probe encapsulation of guests in self-assembled tetraurea calix[4]arene dimers in organic solvents and to demonstrate their destruction by DMSO.

"Container molecules",[1] capable of encapsulating other molecules, have recently emerged as an important theme in supramolecular chemistry. Rebek and de Mendoza have shown that capsules can be formed by the dimerization of curved or concave molecule *via* hydrogen bonds.[2] In particular, such container molecules can be obtained in apolar solvents by dimerization of calix[4]arene derivatives[3] substituted by four urea functions at their "wider rim".[4,5] A recent crystal structure and a detailed NMR study have both confirmed the dimeric nature of these species.[6a,b] From NMR studies in benzene the new peak at ~4.2 ppm has been identified as that of the encapsulated benzene and it has been shown that under certain conditions benzene induces dimerization.[4a,6b]

With the increase in the complexity of the systems prepared in organic supramolecular chemistry there is a constant need for new analytical tools for their characterization. Recently, we have demonstrated the utility of NMR diffusion measurements, as obtained by the pulse gradient spin echo (PGSE)[7] technique, in organic supramolecular chemistry.[8] Therefore, we sought to use this technique to study the dimerization and the encapsulation processes of tetraurea calix[4]arenes.

The diffusion coefficient should, in principle, be a valuable parameter for determining host–guest interactions in general and encapsulation processes in particular since the encapsulated molecules are distinctly smaller than the molecular capsules.[3,6] As such, one should expect the two molecular species to differ considerably in their diffusion coefficients. However, if a small molecule is encapsulated by a large molecule, it should have a much smaller diffusion coefficient than in its free state. In fact, in a situation of slow exchange on the NMR timescale the diffusion coefficient of the small encapsulated species should be equal to that of the large capsule.

In order to demonstrate this point we have measured the diffusion coefficients of dimers **1·1** and **2·2**[6c] in benzene-d_6, in 80:20 (v/v) benzene–benzene-d_6 and in a benzene-d_6 solution containing 2–3% of DMSO-d_6 (Fig. 1, Table 1).†

We have found, as expected, that the diffusion coefficients of the dimers **1·1** and **2·2** are much lower than that of the "free" benzene. Interestingly, the diffusion coefficients of the peaks at 4.4 and 4.1 ppm, previously attributed to the encapsulated benzene, were much lower as compared to that of the "free" benzene. In fact, these values were equal, within experimental

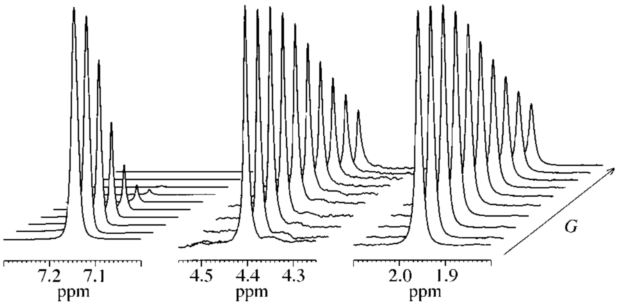


Fig. 1 500 MHz ^{1}H NMR spectra of the Stejskal and Tanner diffusion experiment of **1** in a 80:20 (v/v) benzene–benzene-d_6 solution showing the signal intensity decay as a function of the pulsed gradient strength (*G*). For clarity only the signal of **1** at 1.95 ppm and the signals attributed to "free" and encapsulated benzene at 7.15 and 4.4 ppm, respectively are shown.

Table 1 Diffusion coefficients (in cm^2 s^{-1}) of the peaks attributed to "free" and encapsulated benzene and of the calix[4]arene derivatives in different solutions at 25 °C[a]

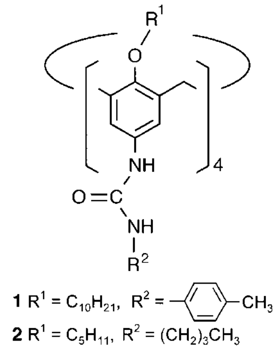
Systems	Peak at 7.15 ppm "free" C_6H_6	Peak attributed to "encapsulated" C_6H_6	Calix[4]arene peak
1 in C_6D_6	$2.08 \pm 0.02 \times 10^{-5}$[b]	—	$0.32 \pm 0.01 \times 10^{-5}$
1 in 80:20 (v/v) C_6H_6–C_6D_6	$2.21 \pm 0.02 \times 10^{-5}$[c,d]	$0.34 \pm 0.01 \times 10^{-5}$	$0.34 \pm 0.01 \times 10^{-5}$
1 in C_6D_6 + ~2% DMSO	$2.08 \pm 0.01 \times 10^{-5}$	—	$0.41 \pm 0.01 \times 10^{-5}$
2 in C_6D_6	$2.07 \pm 0.01 \times 10^{-5}$[b]	—	$0.38 \pm 0.01 \times 10^{-5}$
2 in 80:20 (v/v) C_6H_6–C_6D_6	$2.14 \pm 0.01 \times 10^{-5}$[c,d]	$0.51 \pm 0.01 \times 10^{-5}$[e]	$0.47 \pm 0.01 \times 10^{-5}$[e]
2 in C_6D_6 + ~3% DMSO	$2.09 \pm 0.02 \times 10^{-5}$	—	$0.46 \pm 0.02 \times 10^{-5}$

[a] All numbers are averages ± standard deviation of the mean of three measurements. For experimental details see ref. 8 and footnote †. [b] Values for C_6D_5H in C_6D_6. [c] Values for C_6H_6 in 80:20 (v/v) C_6H_6–C_6D_6 solutions. [d] The diffusion coefficient of benzene at 25 °C was found to be 2.21×10^{-5} cm^2 s^{-1}.[9] [e] Due to the limited solubility of **2·2** in benzene solution, some precipitation did occur during the NMR diffusion experiments. Therefore, it may be that these values are somewhat higher than the real ones. Nevertheless, they are much lower than that of "free" C_6H_6.

Table 2 Diffusion coefficients (in cm^2 s^{-1}) of DMSO molecules in benzene-d$_6$ solutions prior to and after addition of a 5 mM solution of **1**[a]

System	Peak at 7.15 ppm "free" C_6H_6	DMSO peak	Calix[4]arene peaks	
			at 2.1 ppm	at 8.5 ppm
1.4% DMSO in C_6D_6	$2.12 \pm 0.01 \times 10^{-5}$	$2.10 \pm 0.01 \times 10^{-5}$	—	—
1.4% DMSO in C_6D_6 and 5 mM in **1**[b]	$2.12 \pm 0.01 \times 10^{-5}$	$1.93 \pm 0.01 \times 10^{-5}$	$0.34 \pm 0.01 \times 10^{-5}$	$0.35 \pm 0.01 \times 10^{-5}$
2.3% DMSO in C_6D_6	$2.12 \pm 0.01 \times 10^{-5}$	$2.06 \pm 0.01 \times 10^{-5}$	—	—
2.3% DMSO in C_6D_6 and 5 mM in **1**[b]	$2.12 \pm 0.01 \times 10^{-5}$	$1.97 \pm 0.01 \times 10^{-5}$	$0.39 \pm 0.01 \times 10^{-5}$	$0.40 \pm 0.01 \times 10^{-5}$

[a] All measurements were performed at 25 °C. Values are means ± standard deviations of three experiments. [b] Since the diffusion coefficients of benzene after addition of **1** were found to be somewhat lower than those obtained in the blank solutions, the ratios of these two values were used to correct the experimental values.



error, to the diffusion coefficients of the dimers suggesting that in terms of translational diffusion the dimers and the molecular species represented by these peaks are one supramolecular entity. These results corroborate in an independent way the assignment of the peaks at 4.4 and 4.1 ppm as encapsulated benzene in dimers **1·1** and **2·2**, respectively.

In additional experiments we studied the 1D NMR spectra and the diffusional characteristics of *p*-xylene-d$_{10}$ solutions of **1·1** to which we added 10 equivalents of benzene, 1,2-difluorobenzene, hexafluorobenzene or simultaneously 10 equivalents of benzene and 1,2-difluorobenzene or benzene and hexafluorobenzene. In these experiments we found that the NH peak around 9.7 ppm in the NMR spectrum of the dimer of **1·1** is sensitive to the nature of the encapsulated guest.[4a,b,6b] Since the encapsulated guests are in slow exchange, on the NMR timescale, simple integration of these peaks enabled the determination of the affinity of the different guests toward the inner cavity of the dimer **1·1**.‡ As expected, all the signals of the encapsulated guests were found to have very similar diffusion coefficients, within experimental error.

The data in Table 1 also demonstrate that addition of only 2–3% of DMSO to the benzene solutions dissociates the dimers into their monomeric components.[6b] Although the viscosity of the benzene solution increased slightly by the addition of DMSO, there is an increase in the diffusion coefficients of **1** and **2** following the addition of DMSO. The only plausible explanation for these observations is the dissociation of the dimers to the respective monomers, which because of their lower molecular weight should have a higher diffusion coefficient than the respective dimer.

In order to study further the interaction of DMSO molecules with dimer **1·1**, a series of diffusion measurements were performed in which the tetraurea calix[4]arene **1** was added to benzene solutions containing different amounts of DMSO.§ Prior to the addition of **1** the diffusion characteristics of these solutions were determined. The presence of compound **1** should have and had only a small effect on the viscosity of the solutions and hence the diffusion coefficient of the benzene molecule should remain constant. However, experimentally we have found a small decrease in the diffusion coefficient of benzene upon addition of **1**, while a more pronounced decrease in the diffusion coefficient of the DMSO molecule was observed (Table 2). From the changes in the diffusion coefficients of the DMSO molecules in these mixtures upon addition of **1**, bound fractions of about ~11% and ~6% were calculated for DMSO in the benzene solutions containing 1.4% and 2.3%, respectively. In 5 mM benzene solution of compound **1** containing 1.4% or 2.3% DMSO there are around 37 and 62 DMSO molecules, respectively per each molecule of **1**. The calculated bound fractions in the above solutions indicate that an average of about 4 molecules of DMSO are interacting with each molecule of **1**, practically one DMSO molecule for each urea group.

In conclusion, we have demonstrated that NMR diffusion measurements are a valuable tool for probing molecular interactions between organic molecules. This holds for systems where the exchange is slow on the NMR timescale, as in the case of encapsulated guest molecules in a dimer as well as for systems with rapid exchange, as in the case of DMSO molecules bound to the "monomeric" tetraurea.

Notes and references

† Diffusion experiments were carried out on a 500 MHz ARX Bruker (Karlshruhe, Germany) NMR spectrometer equipped with a B-AFPA10 pulsed gradient unit capable of producing a *Z*-gradient of about 50 G cm^{-1}. All experiments were carried out in a 5 mm inverse probe with pulse gradients of 2 ms and a pulse gradient separation of 62 ms. The total echo time was 124 ms and the pulsed gradients were incremented from 0 to 46.8 G cm^{-1} in ten steps. The experiments were performed at least three times and only data for which the correlation coefficient (*R*) was higher than 0.999 were included. In the 80:20 (v/v) benzene–benzene-d$_6$ solutions, because of the large singlet of the C_6H_6, two different sets of experiments were performed in order to extract the different diffusion coefficients. While the diffusion coefficient of C_6H_6 was extracted from simple PGSE experiments, the diffusion coefficients of all other species were extracted from a PGSE experiment in which the singlet of the "free" benzene was suppressed by a long (100 ms) low power RF pulse.

‡ From these experiments we concluded that the relative affinity of 1,2-difluorobenzene, benzene, hexafluorobenzene and xylene guests toward the dimer cavity are approximately 750:600:25:1, respectively.

§ Although the DMSO was treated with molecular sieves (sodium alumina–silicate type 4A, BDH Chemicals), a water peak was observed in the spectrum. The amounts of water increased with the increase of the amount of DMSO and were found between 0.2% and 0.4% relative to benzene. However, it seems that at these experimental conditions the water molecules do not contribute significantly to the disruption of the dimer.

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