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Thio-ether-footed resorcin[4]arenes: self-assembly in solution and interaction with gold nanoparticles as viewed by diffusion NMR

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ABSTRACT

In this paper we present the synthesis and characterization of a new family of thio-ether-footed resorcin[4]arenes (**2**–**4**). Diffusion NMR was used to follow the self-assembly of **2**–**4** in $CDCl_3$ and $CHCl_3$ solutions. We found that all three molecules self-assemble into hexameric capsules. These capsules can accommodate both tertiary alkylamines and ammonium salts. From the diffusion NMR data we could conclude that the hexameric capsules of compounds **2**–**4** are of nearly equal stability and prevail in other organic solvents, such as dichloromethane and benzene but not in tetrahydrofuran (THF). By measuring the diffusion coefficients of **2**–**4** in different concentrations, we found that further aggregation, beyond the hexameric aggregates, is obtained, especially in the case of **2** at high concentrations. Different diffusion NMR techniques revealed that water molecules are part of the hexameric capsules of **2**–**4** in chloroform solutions. In addition diffusion NMR was used to examine the interactions of compounds **2**–**4** with gold nanoparticles in chloroform solution and provided an unequivocal evidence for the attachment of **2**–**4** to the surface of gold nanoparticles. No evidence was found for the formation of higher aggregates on the gold nanoparticles.

1. Introduction

Self-assembled molecular capsules in general, and hydrogen-bonded molecular capsules in particular, have attracted much interest in the last decade.[1,2] Dimeric and hexameric hydrogen-bond capsules have been studied in the solid state, in solution, and very recently in the gas phase.[3–6] Atwood and Mattay were the first to demonstrate that resorcin[4]arenes and pyrogallol[4]arenes such as compounds **1a**–**f** form hexameric capsules in the solid state[4] (Scheme 1).

Rebek demonstrated that **1b** also forms hexameric capsules in solution in the presence of specific guests[5a,c] whereas Avram and Cohen, with the aid of diffusion NMR, demonstrated that both resorcin[4]arenes (**1a** and **1b**) and pyrogallol[4]arenes (**1e** and **1f**) self-assemble into hexameric capsules in organic solvents even in the absence of specific guests.[5d–h]

Diffusion NMR[7] has been found to be an invaluable tool for studying supramolecular systems in solution in general,[8] and for the characterization of molecular capsules in particular.[5d–h,9–11] Diffusion NMR was used to study hydrogen-bonded dimeric capsules[10] and demonstrated unequivocally that systems such as **1a**, **1b**, **1e**, and **1f** self-assemble spontaneously into hexameric capsules in organic solvents.[5d–h,11] For example, with the aid of diffusion NMR it was possible to show that **1a** and **1b** form a $[(\mathbf{1})_6(H_2O)_8]$-type hexameric capsules, whereas **1e** and **1f** form a $(\mathbf{1})_6$-type capsules.[5e,g] Recently, it was demonstrated that specific alcohols may replace the water molecules.[12] Diffusion NMR was also instrumental in characterizing different host–guest complexes of such systems, demonstrating, for example, that several 1:1 and 1:2 host–guest complexes of **1b** are in fact hexameric capsules encapsulating a multiplicity of guest molecules.[13] It was demonstrated that the 1:1 and 1:2 host–guest complexes of **1b** with glutaric acid **5** (Scheme 2) and β-methyl-D-glucopyranoside **6** (Scheme 2), originally prepared by Aoyama's group,[14] are in fact hexameric capsules encapsulating six and three molecules of **5** and **6**, respectively.[13] Recently we could show that calixpyridine[4]arenes **7**[15] (Scheme 2) also form hexameric capsules.[16] In this study the hexamer, dimer, and monomer of **7** were identified with diffusion NMR.[16] Diffusion NMR showed that the self-assembly of **1a** and **1f** and of **1b** and **1e** proceed with self-sorting and that no heterohexamers are formed.[5h] For **1a** and **1b** as well as **1e** and **1f**, however, heterohexamers were formed within hours after mixing.[5h] Recent studies showed that at much lower concentrations these processes are much faster.[17] Atwood and others demonstrated that encapsulation in such systems may affect the properties of encapsulated guests.[18,19]

Recently it was demonstrated that thio-ether-footed systems such as **8** (Scheme 2) can form dimers on planar gold surfaces.[20]

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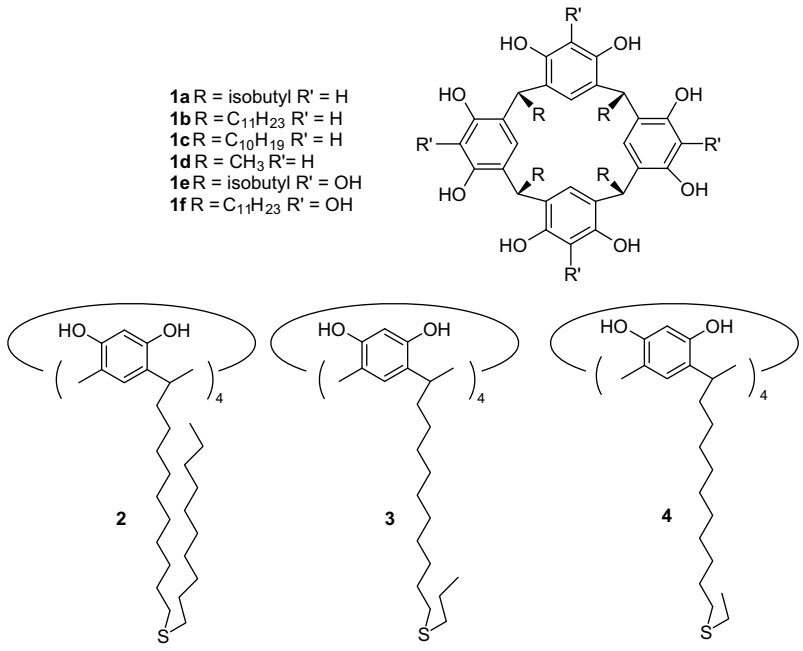
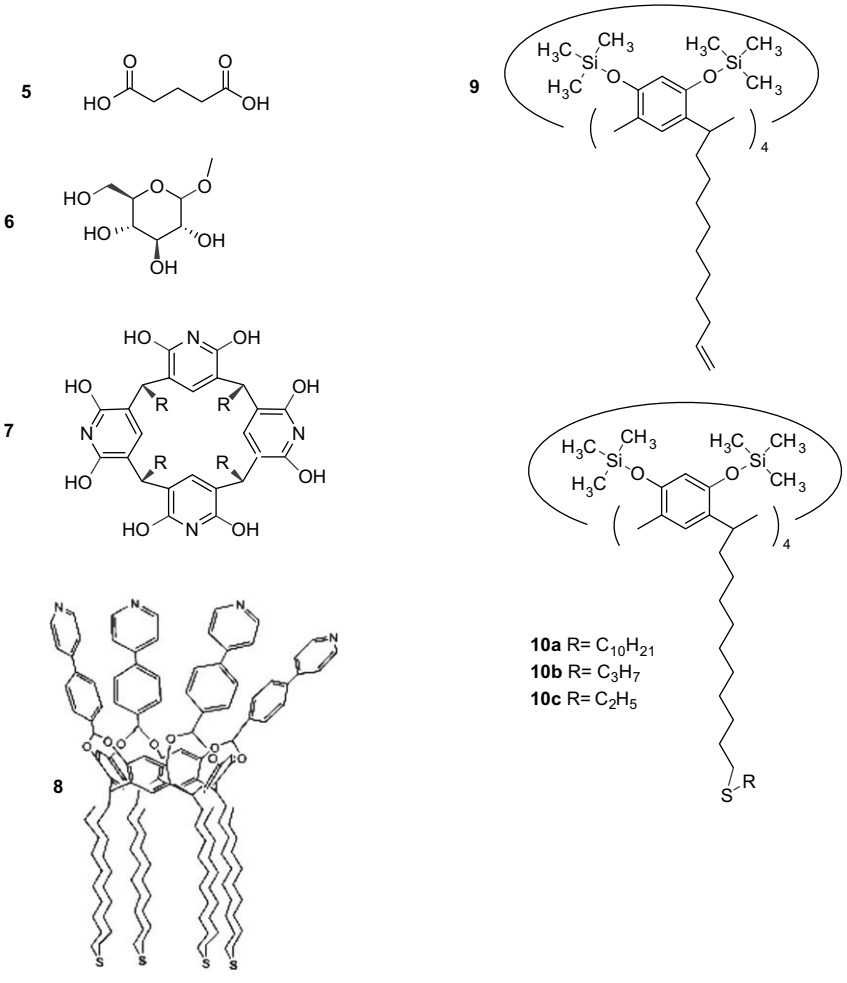


Scheme 1.



Scheme 2.

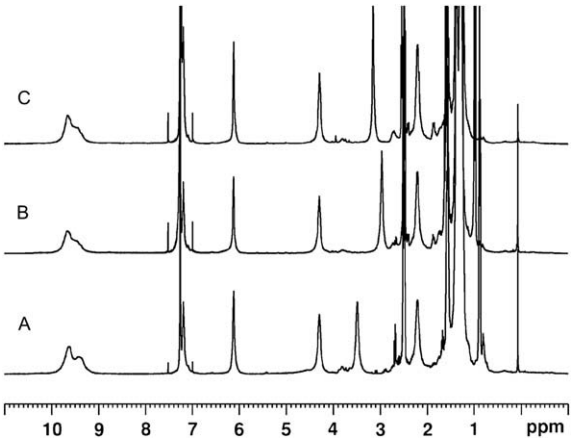


Figure 1. ^{1}H NMR spectra (400 MHz, 298 K) of 20 mM $CDCl_3$ solutions of (A) **2**, (B) **3**, and (C) **4**.

Table 1
Diffusion coefficients of **1b**, **2**, **3**, and **4** in chloroform solutions at 298 K

System	Diffusion coefficients [$\times 10^5$ cm^2 s^{-1}]			
	1b	**2**	**3**	**4**
[M_w][a]	1104 gr mol^{-1}	1737 gr mol^{-1}	1344 gr mol^{-1}	1288 gr mol^{-1}
20 mM $CDCl_3$	0.24±0.01	0.17±0.01	0.20±0.01	0.22±0.01
20 mM $CHCl_3$	0.27±0.01	0.17±0.01	0.20±0.01	0.20±0.01
	0.27±0.01[b]	0.17±0.01[b]	0.22±0.01[b]	0.19±0.01[b]

[a] Molecular weights of the monomers.
[b] The diffusion coefficient of the encapsulated chloroform molecules.

Here we decided to synthesize compounds **2**–**4**, study their self-assembly in solution, and characterize their interaction with gold nanoparticles by diffusion NMR.

2. Results and discussion

2.1. Synthesis of the macrocycles

Compounds **2**–**4** were prepared according to modifications of a procedure previously published.[20] The first step was the acid-catalyzed condensation of resorcinol and undecylenic aldehyde to yield **1c**, which was followed by the protection of the hydroxyl moieties of **1c** by trimethylsilane groups to obtain compound **9** (Scheme 2). This was done to avoid a reaction between 9-BBN and the hydroxyls of **1c**, and was achieved by reacting **1c** with chlorotrimethylsilane in the presence of triethylamine at room temperature. The next step was the anti-Markovnikov addition to **9** of 1-decanethiol, 1-propanethiol, and 1-ethanethiol in the presence of a stoichiometric quantity of 9-BBN in THF at room temperature to form **10a**–**c** (Scheme 2), respectively. Finally, the silane groups of **10a**–**c** were removed with concentrated HCl in methanol, and the desired resorcin[4]arenes **2**, **3**, and **4** were obtained, respectively. The ^{1}H NMR spectra of **2**, **3**, and **4** in $CDCl_3$ are shown in Figure 1. Compounds **2**–**4** were obtained in overall yields of 45%, 38%, and 37%, respectively.

2.2. Self-assembly in solution

Table 1 shows the diffusion coefficients of **1b**, **2**, **3**, and **4** in chloroform solutions at a concentration of 20 mM. The diffusion coefficients of **2**–**4** are not very different and are all lower than that of **1b**, which is consistent with the higher molecular weights of **2**–**4** as compared to **1b** (Table 1). After adding CD_3OD, a significant increase in the diffusion coefficients was observed for all three macrocycles, as was previously found for **1b**.[5d,h] This similar behavior indicated that just like **1b**, **2**–**4** also self-assemble spontaneously into hexameric capsules in chloroform solutions.

The ^{1}H NMR spectra of **1b** and **2**–**4** in $CHCl_3$ are shown in Figure 2. When **2**–**4** were dissolved in $CHCl_3$, the same spectra were obtained as in $CDCl_3$ with additional signals in the range of 4.8–5.1 ppm, which are about 2 ppm upfield from the signals of bulk chloroform. These new peaks had the same diffusion coefficients as those of the macrocycle (Table 1), and therefore they were attributed to the encapsulated chloroform molecules, as was previously determined for **1b**.[5d–g] From the integration of the encapsulated chloroform peaks in the ^{1}H NMR spectra, we concluded that about four chloroform molecules are encapsulated in the hexamers of **2**–**4**.

The peaks of the encapsulated chloroform molecules in the case of **2**–**4** are not as sharp as those of the signals of the encapsulated

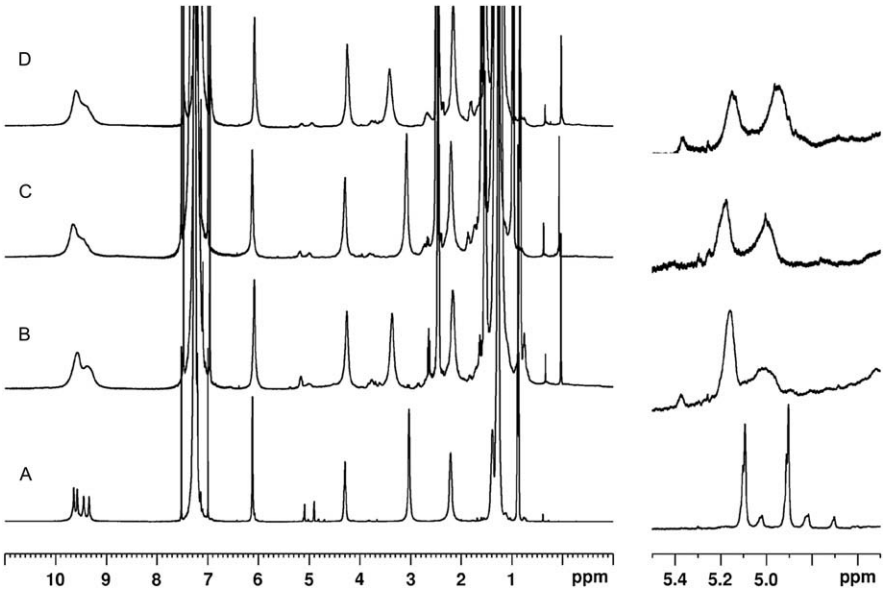


Figure 2. ^{1}H NMR spectra (400 MHz, 298 K) of 20 mM $CHCl_3$ solutions of (A) **1b**, (B) **2**, (C) **3**, and (D) **4**. The peaks on the right are magnifications of the signals of the encapsulated chloroform molecules.

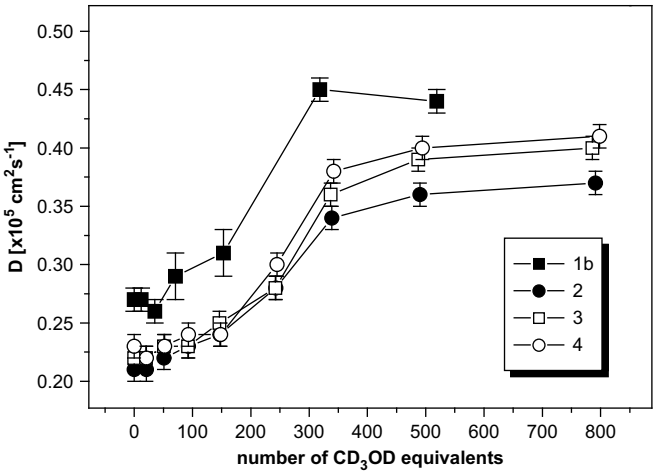


Figure 3. Changes in the diffusion coefficients of **1b** (■), **2** (●), **3** (□), and **4** (○) (in a 3 mM $CDCl_3$ solution, 298 K) as a function of the number of equivalents of CD_3OD added to the $CDCl_3$ solution.

chloroform in the hexameric capsules of **1b** (compare Fig. 2B–D and Fig. 2A). This may indicate that the hexameric capsules of **2**–**4** are slightly different from the hexameric capsules of **1b**. Apparently the chloroform molecules have different dynamics inside the capsules of **2**–**4**, as compared with the capsule of **1b**. Another plausible explanation is that the capsules of **2**–**4** are looser and the exchange between free and encapsulated chloroform molecules is therefore faster. To examine the latter explanation we used diffusion NMR to study the relative stability of the molecular capsules of **2**–**4** in chloroform solutions. For this purpose, we followed the changes in the diffusion coefficients of the macrocycles after adding different amounts of CD_3OD. Figure 3 shows the changes in the diffusion coefficients of **2**–**4** as a function of the CD_3OD equivalents added to their chloroform solutions, along with the changes in the diffusion coefficient observed for **1b**, under the same experimental conditions.

Methanol is a protic solvent that can break the intermolecular hydrogen bonds in these hexameric capsules and convert them into their respective monomeric species. This disaggregation can be easily followed by diffusion measurements since the monomers diffuse more rapidly than the respective hexamers due to the large difference in their molecular weight. Indeed, as a result of these titrations, an increase in the diffusion coefficients of all four macrocycles was observed. According to Figure 3, nearly the same amount of CD_3OD was needed to obtain the plateau value of the diffusion coefficient for compounds **2**–**4**. These results indicate that **2**–**4** form hexameric capsules that are based on hydrogen bonds, just like **1b**, and that the relative stability of these aggregates is very similar. This conclusion is reasonable since all four macrocycles have the same number of OH moieties, which are responsible for the formation of the hexameric capsules of these systems, probably by similar intermolecular networks of hydrogen bonds.

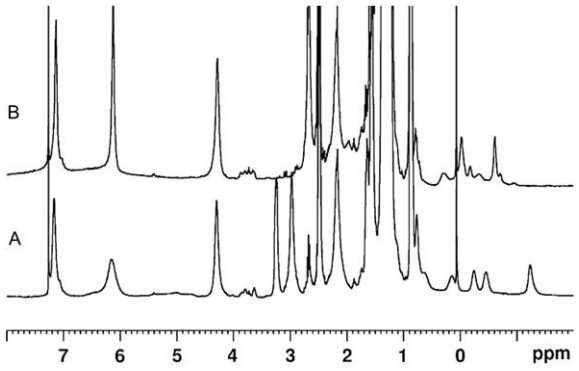


Figure 4. ^1H NMR spectra (400 MHz, 298 K) of 20 mM $CDCl_3$ solutions of **2** in the presence of (A) tetrahexylammonium bromide (THABr) and (B) trihexylamine (THA). The ratio between **2** and the guests (free and encapsulated) is 6:3.

We also measured the diffusion coefficients of macrocycles **2**–**4** in different organic solvents, and compared the extracted values to those obtained for **1b**, under similar experimental conditions, and the results are presented in Table 2.

The relatively low diffusion coefficients of all four macrocycles imply that systems **2**–**4** self-assemble into hexameric capsules in chloroform, dichloromethane, and benzene. However, in THF, clearly there is a large increase in the diffusion coefficients of all four macrocycles, implying that THF converts the hexameric capsules of **2**–**4** into their respective monomeric species. These results show that resorcin[4]arene with different alkyl chains on the methine bridge, self-assemble spontaneously into hexameric capsules in different organic solvents and that no specific guest is needed to induce the formation of these hexameric capsules.

We found that the hexamer of **1b** can accommodate both neutral tertiary alkylamines and charged quaternary alkylammoniums [21] and we wanted to determine whether the capsules of **2**–**4** can also encapsulate such guests. Figure 4 shows the ^1H NMR spectra of **2** in $CDCl_3$ after adding tetrahexylammonium bromide (THABr) (Fig. 4A) and trihexylamine (THA) (Fig. 4B). After the guests were added to the $CDCl_3$ solution of **2**, high-field chemical shift peaks of the encapsulated alkylammonium salt and the alkylamine appeared (Fig. 4A and B, respectively). In both cases, the diffusion coefficients of the new signals in the higher field were the same, within experimental errors, as those of **2** (Table 3). The integral ratio between these signals and the signals of **2** indicated a 1:6 ratio between the encapsulated guest and the host. This ratio is a further proof for the formation of a hexameric capsule in chloroform solutions, which encapsulates one guest molecule of either an amine or an ammonium salt.[5a]

These guests were also encapsulated within the capsules of **3** and **4** and the diffusion coefficients of the macrocycle and the encapsulated guests were very similar (see Table 3).

The results presented in Table 3 indicate that the guest affinities of the hexameric capsules of resorcin[4]arenes are unaffected by

Table 2
Diffusion coefficients of **1b**, **2**, **3**, and **4** (15–20 mM) in different solvents at 298 K

System	Diffusion coefficients [$\times 10^5$ cm^2 s^{-1}]			
	1b	**2**	**3**	**4**
[M_w][a]	1104 gr mol^{-1}	1737 gr mol^{-1}	1344 gr mol^{-1}	1288 gr mol^{-1}
$CDCl_3$	0.24±0.01	0.17±0.01	0.20±0.01	0.22±0.01
CD_2Cl_2	0.29±0.01	0.24±0.01	0.28±0.01	0.28±0.01
C_6D_6	0.18±0.01	0.16±0.01	0.18±0.01	0.18±0.01
THF-d_8	0.50±0.01	0.44±0.01	0.45±0.02	0.45±0.01

[a] Molecular weights of the monomers.

Table 3
Diffusion coefficients of **2**, **3** and **4** (20 mM) in $CDCl_3$, in the presence of THA and THABr

System	Diffusion coefficients [$\times 10^5$ cm^2 s^{-1}]			
	THA		THABr	
	Encapsulated guest	Macrocycle	Encapsulated guest	Macrocycle
2	0.15±0.01	0.16±0.01	0.17±0.01	0.18±0.01
3	0.18±0.01	0.20±0.01	0.21±0.01	0.20±0.01
4	0.20±0.01	0.20±0.01	0.22±0.02	0.22±0.01

the nature of the alkyl chains on the methine bridges or by the lipophilicity of the macrocycles.

The ratio between the diffusion coefficients of two species is a function of their molecular weights, and is generally given by the relationships presented in Eq. 1:[7c]

$$\sqrt[3]{\left(\frac{M_i}{M_{1b}}\right)} \le \frac{D_{1b}}{D_i} \le \sqrt{\frac{M_i}{M_{1b}}} \quad (1)$$

When applying the molecular weights of **2**–**4** (M_i) relative to the molecular weight of **1b** (M_{1b}) to Eq. 1, the ratios of the experimental diffusion coefficients are higher than the expected ratios for these macrocycles. The deviation from the expected ratios of the diffusion coefficients of **2**–**4** and **1b** increases as the length of the alkyl chains on the methine bridges increases. Therefore we suspected that for longer alkyl chains further aggregation is obtained. To examine this assumption, we measured the diffusion coefficients of **1b** and **2**–**4** in increasing concentrations and the results are presented in Figure 5.

According to Figure 5, as the concentration is increased, there is a decrease in the diffusion coefficients of all four macrocycles, but not to the same extent. The smallest effect of the concentration on the diffusion coefficient is observed for **1b**. The decrease in the diffusion coefficients of **3** and **4**, as the concentration increases, is quite similar and not very different from the decrease observed for **1b**. These small decreases in the diffusion coefficients, as the concentration increases, may be due to an increase in the viscosity of the solution, which is not unusual at large concentrations. The most significant decrease in the diffusion coefficient was observed for **2**, which also has the longest alkyl chain on the methine bridge of the resorcin[4]arene skeleton. The diffusion coefficient of **2** decreased by almost 50%, from $0.21\pm0.01\times10^{-5}$ $cm^2\,s^{-1}$ to $0.12\pm0.01\times10^{-5}$ $cm^2\,s^{-1}$. These results indicate that in addition to the formation of hexameric capsules, further aggregation prevails in solution, especially in the case of highly concentrated chloroform solutions of **2**. In each hexamer, there are 24 long alkyl chains, each containing 21 carbons. These chains can, in principle, create aggregates, which are stabilized by multiple Van der Wals interactions.

Previously we found, by diffusion NMR, that **1b** self-assembles into a hexameric capsule with eight water molecules in chloroform solutions.[5e–g] We also showed that for water molecules that exchange between two sites that differ considerably in their diffusion coefficients, the signal decay extracted from pulsed gradient spin echo (PGSE)[7a] and pulsed gradient stimulated echo (PGSTE)[22a] diffusion sequences differs from the signal decay extracted from the longitudinal eddy current delay (LED)[22b] and the bipolar LED (BPLED)[22c] diffusion sequences.[23] We also found that the additional extra diffusion component in the non-mono-exponential signal decay develops during the eddy current delay (the t_e period) of the LED and BPLED sequences.[23] As this delay is increased, the extra component of the signal decay becomes more pronounced. We suggested that in such systems, the non-mono-exponential signal decay in the LED experiment at different t_es, can serve as a good indication of the role of water molecules in such supramolecular hexamers.[23] Therefore, we decided to use this approach to examine the role of water molecules in the self-assembly of **2**–**4**. Figure 6

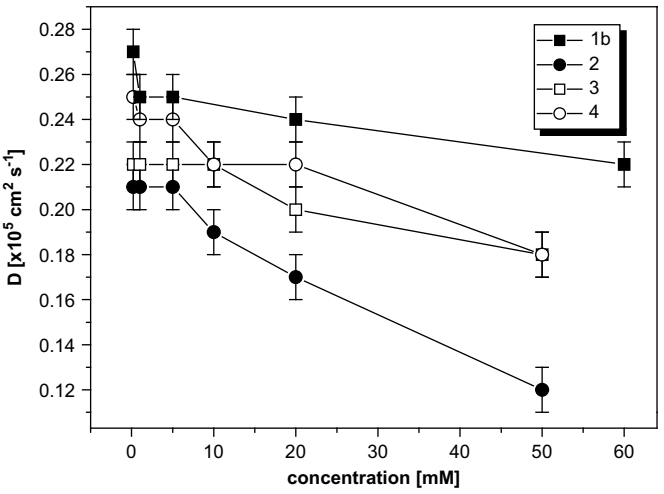


Figure 5. The diffusion coefficients of **1b** (■), **2** (●), **3** (□), and **4** (○) (in a $CDCl_3$ solution, 298 K) as a function of their concentration.

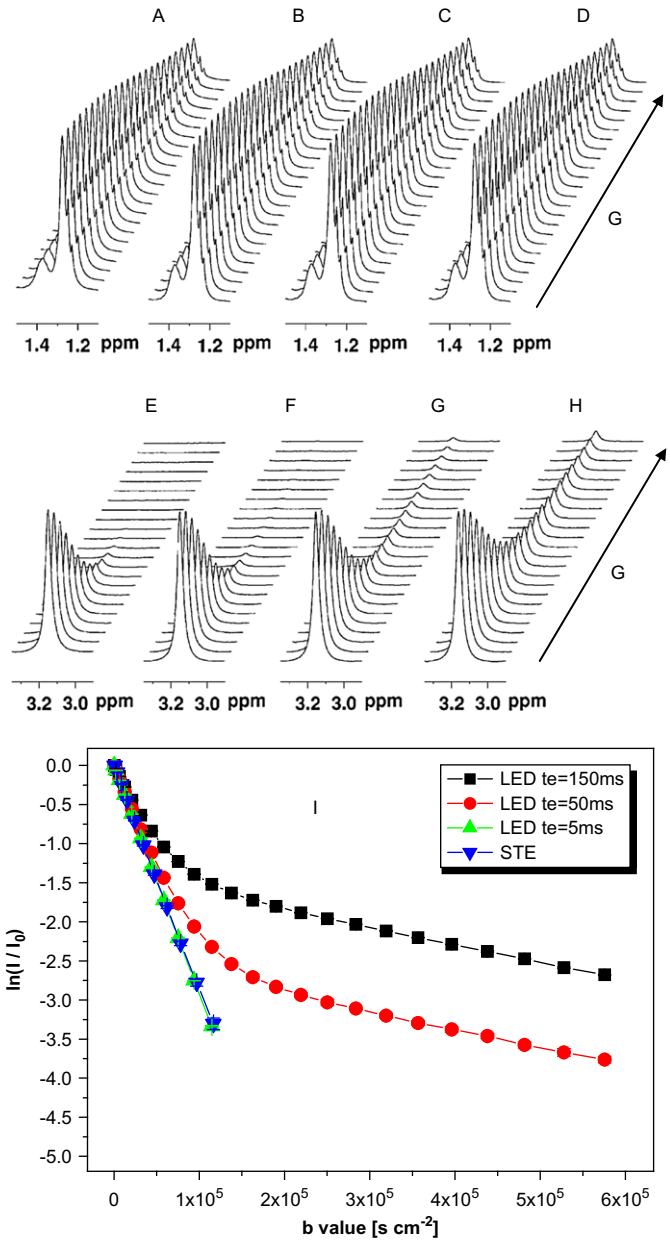


Figure 6. ^1H NMR signal decay as a function of the gradient strength (G) (400 MHz, 298 K) of one of the peaks of **4** (A–D) and the water peak (E–H) in a 20 mM $CDCl_3$ solution of **4**, as extracted from the PGSTE diffusion sequence (A and E) and the LED sequence with the following t_es: (B and F) 5 ms, (C and G) 50 ms, and (D and H) 150 ms. (I) is the ln of the normalized signal decay ($\ln I/I_0$) as a function of the b value for water in a $CDCl_3$ solution of **4**, as extracted from the LED diffusion sequence with different t_es and the PGSTE diffusion sequence.

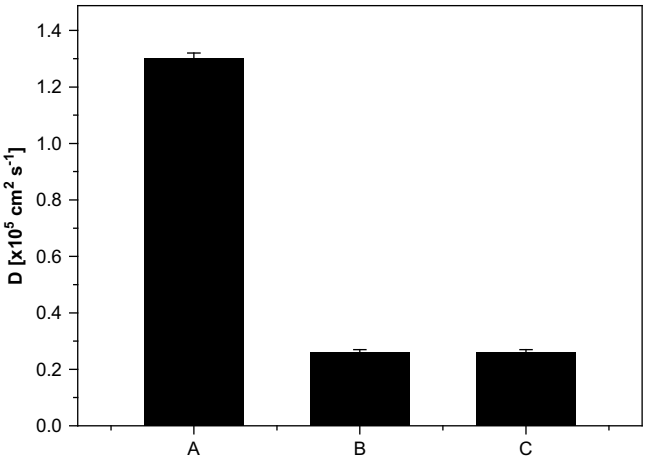


Figure 7. Diffusion coefficients of the peaks of 1-decanethiol in different forms in $CDCl_3$: (A) free decanethiol, (B) decanethiol attached to gold nanoparticles, and (C) after the addition of CD_3OD to (B).

shows the signal decay of one of the peaks of **4** (A–D), and the water peak (E–H) in a 20 mM $CDCl_3$ solution of **4** as extracted from the PGSTE diffusion sequence and the LED sequence with different t_es.

This figure shows that the signal decay of **4** was not affected by the increase in the t_e delay (Fig. 6A–D), as opposed to the water signal decay (Fig. 6E–H).

For the PGSTE and the LED sequence with a short t_e of 5 ms, similar water signal decay was observed (Fig. 6E,F, and I). This indicates that, indeed, by using a relatively short t_e, the LED sequence is degenerated into a PGSTE-like sequence, resulting in a mono-exponential signal decay as expected. However, by increasing the t_e, an additional diffusion component of the water signal can be observed (Fig. 6G,H, and I). Very similar results were obtained for $CDCl_3$ solutions of **2** and **3** (data not shown). These results indicate that in solutions of **2**–**4**, there is an exchange between different populations of the water molecules having very different diffusion coefficients. Therefore, we can conclude that for **2**–**4**, as was previously found for other derivatives of resorcin[4]arenes,[23] water molecules are part of the self-assembled hexameric capsules found in chloroform solutions.

2.3. Interaction with gold nanoparticles

So far we have used diffusion NMR to study the self-assembly of the new thio-ether-footed resorcin[4]arenes in different organic solvents. It is well known that different alkanethiols are used in the preparation of gold nanoparticles. The thiols bind covalently to the gold and hence protect the nanoparticles, provide them with solubility in organic solvents, and prevent their aggregation over time.[24] Our next goal was to use diffusion NMR to study the interaction and the self-assembly of such systems on the surface of gold nanoparticles. The nanoparticles were prepared according to the phase transfer procedure of Brust and Schiffrin from the early 90s.[25] We prepared different thio-ether-resorcin[4]arene gold nanoparticles (AuNPs), i.e., **2**·AuNPs, **3**·AuNPs, **4**·AuNPs, and an alkylthiol ($C_{10}H_{21}SH$)·AuNPs, which was used as a reference. We measured the diffusion coefficients of the different thio-ether-resorcin[4]arene nanoparticles, along with the ($C_{10}H_{21}SH$)·AuNPs reference, in $CDCl_3$ solutions. These measurements were performed to verify whether compounds **2**–**4** are attached to the surface of the nanoparticles, in order to probe the diffusion coefficient of the gold nanoparticles, and to study if one can observe further interactions between the nanoparticles or even if higher aggregates can be identified on the nanoparticles surface. First we measured the diffusion coefficients of ($C_{10}H_{21}SH$)·AuNPs and the value that was extracted was five times lower than the diffusion coefficient of free 1-decanethiol (Fig. 7B and A, respectively). This decrease in the diffusion coefficient of decanethiol demonstrates the binding of the thiol to the gold nanoparticles. In fact in the later case, the diffusion

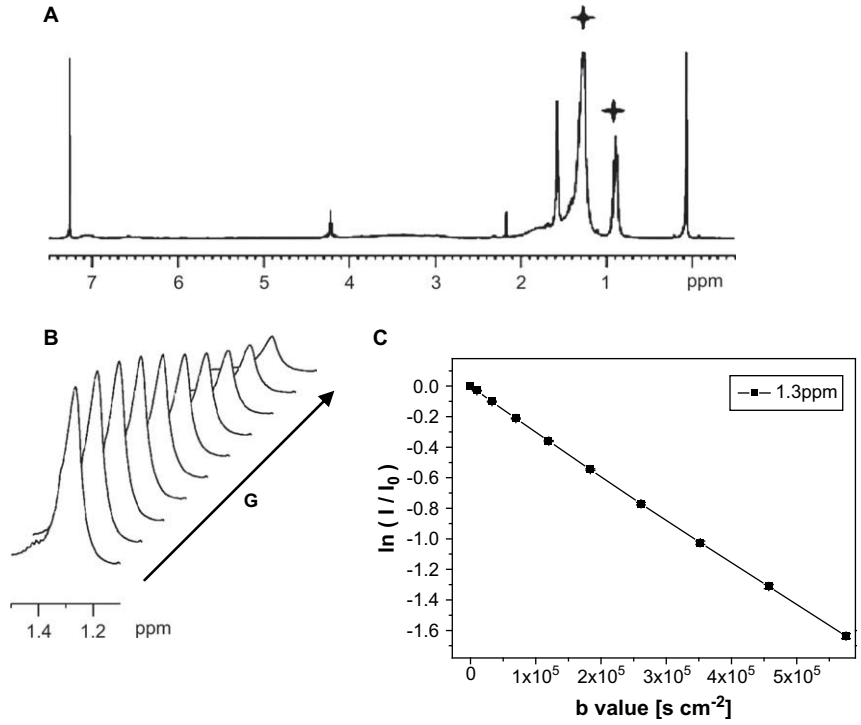


Figure 8. (A) ^{1}H NMR spectrum of **2**·AuNPs in $CDCl_3$. (B) ^{1}H NMR signal decay as a function of the gradient strength (G) of one of the signals of **2**·AuNPs in the solution shown in (A). (C) The natural log of the normalized signal decay shown in (B) as a function of *b* value. The symbol '+' represents the peaks of **2** on the surface of the gold nanoparticle.

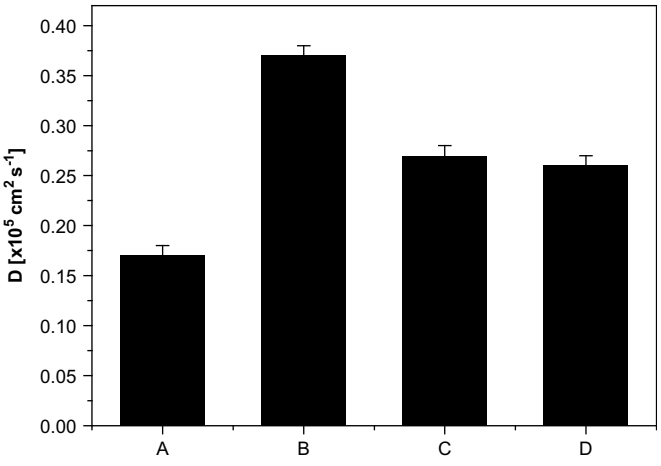


Figure 9. Diffusion coefficients of the peaks of **2** in different forms in $CDCl_3$: (A) 20 mM of **2** (hexamer), (B) after adding CD_3OD to (A) (monomer), (C) **2** attached to gold nanoparticles and (D) after adding CD_3OD to (C).

coefficient of the decanethiol represents the diffusion coefficient of the entire nanoparticle. We added 10% of CD_3OD to the chloroform solution of $(C_{10}H_{21}SH)$·AuNPs, to examine whether such an addition has any effect on the observed diffusion coefficient. This was done since we wanted to use methanol in the study of **2**–**4**·AuNPs (vide infra). Figure 7C shows that the addition of methanol had no effect on the diffusion coefficient of the decanethiol in $(C_{10}H_{21}SH)$·AuNPs.

We repeated these experiments for **2**·AuNPs, **3**·AuNPs, and **4**·AuNPs in chloroform solutions and the results obtained for **2**·AuNPs are shown in Figures 8 and 9. Figure 8A shows the ^{1}H NMR spectrum of **2**·AuNPs and Figure 8B shows the stackplot of one of the signal of **2**·AuNPs as a function of the gradient strength (G). Clearly only some of the signals of the more labile groups of **2** can be observed in the ^{1}H NMR spectrum of **2**·AuNPs. Indeed, the stackplot as a function of G, and the signal decay as a function of the diffusion weighting, b, which are linear and reliable, as shown in Figure 8B and C, enable accurate determination of the diffusion coefficient of **2**·AuNPs. The diffusion coefficient of **2**·AuNPs was $0.27\pm0.01\times10^{-5}$ cm^2 s^{-1}, which is lower than the value extracted for the monomer of **2** ($0.37\pm0.01\times10^{-5}$ cm^2 s^{-1}, Fig. 9B) but higher than the value extracted for the hexamer of **2** ($0.17\pm0.01\times10^{-5}$ cm^2 s^{-1}, Fig. 9A). After adding CD_3OD, there was hardly any change in the diffusion coefficient of **2**·AuNPs (Fig. 9D). These results show that **2** is attached to the gold nanoparticles, however, only as a monomer. There is no indication of the formation of hexamers or even dimers on the surface of the nanoparticles. The fact that methanol had no effect on the extracted diffusion coefficient also indicates that there are no aggregates of **2** in solution. In addition, the decrease in the diffusion coefficients of 1-decanethiol upon attachment to the nanoparticles (factor 5) was much more pronounced than that obtained for **2** (factor 1.4). There are at least two plausible explanations for the above observation. First, it seems that more 1-decanethiol molecules are attached to each nanoparticle, in comparison with **2**. This is very reasonable since for decanethiol, where steric effects are less significant, more molecules may attach to each nanoparticle, as compared with **2**. It may well be that these steric effects are also preventing the formation of higher aggregates on the nanoparticles' surfaces. Another explanation for this observation is that the nanoparticles formed with the thiols are somewhat larger than that obtained when compounds **2**–**4** are used to prepare the gold nanoparticles.

3. Conclusions

We have used diffusion NMR to study the self-assembly of a new family of resorcin[4]arenes (**2**–**4**) in solution. After preparing these molecules, we found that all three compounds (**2**–**4**) self-assemble spontaneously into hexameric capsules in chloroform, dichloromethane, and benzene but not in THF. The relative stability of these capsules is almost the same and is quite similar to that previously found for other derivatives of resorcin[4]arene (**1a** and **1b**). We also found that the hexameric capsules of **2**, **3**, and **4** encapsulate both neutral alkylamines and charged ammonium salts. By using diffusion measurements in different concentrations, we showed that further aggregation prevails in solution at high concentrations, especially in the case of **2**. By measuring diffusion using the LED sequence at different t_es, it was shown that water molecules are part of the hexameric capsule of **2**, **3**, and **4**. In addition, we prepared four different thiol- and thio-ether-coated gold nanoparticles and used diffusion NMR to study the interactions of **2**–**4** with the surfaces of the gold nanoparticles in chloroform solutions. Interestingly, we found that the diffusion coefficients of **2**–**4**·AuNPs are higher than that of $(C_{10}H_{21}SH)$·AuNPs despite the fact that the molecular weight of $C_{10}H_{21}SH$ is significantly lower than the MW of **2**–**4**. No evidence was found for aggregation of **2**–**4** on the surface of the nanoparticles. All these results clearly demonstrate the importance of diffusion NMR in studying such supramolecular systems both in solution and on the surface of gold nanoparticles.

4. Experimental section

4.1. Diffusion NMR

NMR diffusion measurements were performed using a 400 MHz Avance Bruker NMR spectrometer equipped with a Great1 gradient system capable of producing magnetic field pulse gradients in the z-direction of about 50 G cm^{-1}. The diffusion experiments were performed using the stimulated echo diffusion sequence or the LED sequence. All experiments were carried out using a 5 mm inverse probe. For the stimulated echo diffusion experiments, the rectangular pulsed-gradients, of 3 ms of duration, were incremented from 0 to 40.2 G cm^{-1} in 24 steps and the pulse gradient separation was 50 ms. For the LED experiments the sine shape pulsed-gradients, of 4 ms of duration, were incremented from 0.7 to 32.2 G cm^{-1} in 10 or 24 steps and the pulse gradient separation was 50 ms. All measurements were performed at least three times and the reported diffusion coefficients represent the mean±standard deviation of three experiments. Only data where the correlation coefficients of $\ln(I/I_0)$ versus $\gamma^2\delta^2g^2(\Delta-\delta/3)$ were higher than 0.999 are reported. The measurements were all preformed at 298.0 K. All diffusion measurements were performed in a 4 mm NMR tube inserted in a 5 mm NMR tube.

4.2. Materials

All starting materials, guest molecules, reagents, and the deuterated solvents ($CDCl_3$, CD_3OD, CD_2Cl_2, C_6D_6, and THF-d_8) were purchased from Aldrich (USA) and were used as supplied. Compound **1b** was prepared according to modifications of the procedure published previously.[26] Thio-ether-footed resorcin[4]arenes having different thio-ether-groups i.e., **2**, **3**, and **4** were synthesized using a modification of the procedure previously described in the literature.[20]

4.3. Resorcin[4]arene 1c

A solution of 8.5 g (77 mmol) of resorcinol in a solution of 40 ml of 95% ethanol and 12 ml of concentrated hydrochloric acid

was cooled to 2 °C. Undecylenic aldehyde (16 ml, 77 mmol) in 30 ml of 95% ethanol was added dropwise to the solution and was stirred under argon over a period of 2 h. The resulting solution was allowed to slowly warm to 25 °C and then was heated to 75 °C for 21 h. Next the precipitate was washed with 80 ml of water and dried. Finally, the material was crystallized twice from acetonitrile to yield, after drying, 11.9 g (59.5%) of resorcin[4]arene **1c** as an orange powder.

^{1}H NMR of hexameric **1c** (200 MHz, $CDCl_3$, 25 °C, 30 mM): δ=9.59 (br s, 24H, OH), 9.34 (br s, 24H, OH), 7.20 (s, 24H, ArH), 6.12 (s, 24H, ArH), 5.79 (m, 24H; R–CH═CH_2), 4.95 (m, 48H, CH═CH_2), 4.3 (br t, 24H, ArCH), 2.02 (br q, 48H, ArCH–CH_2), 1.30 (m, 336H, $(CH_2)_7$).

4.4. Trimethylsilane protected resorcin[4]arene (9)

Dry NEt_3 (5.6 ml, 40.3 mmol) and $ClSi(CH_3)_3$ (3.64 ml, 28.8 mmol) were added to a solution of resorcinarene **1c** (3 g, 2.88 mmol) in dry THF (20 ml) cooled to −10 °C. The solution was stirred at 0 °C for 2 h and then at room temperature for an additional 16 h. After the solvent was evaporated under vacuum, the brown crude product obtained was purified by flash column chromatography on silica by using CH_2Cl_2/hexane (8:2 v/v) as an eluent to yield the trimethylsilane protected resorcinarene (**9**) as a bright yellow-orange solid (3.54 g, 76%).

^{1}H NMR of monomeric **9** (200 MHz, $CDCl_3$, 25 °C, 30 mM): δ=7.16 (br s, 2H, ArH), 6.28 (br s, 2H, ArH), 6.18 (br s, 2H, ArH), 6.00 (br s, 2H, ArH), 5.77 (m, 4H, R–*CH*═CH_2), 4.95 (m, 8H, CH═C*H*$_2$), 4.3 (br t, 4H, ArCH), 2.02 (br q, 8H, ArCH–*CH*$_2$), 1.71 (m, 8H, R–C*H*$_2$CH═CH_2), 1.25 (m, 48H, $(CH_2)_6$), 0.38 (s, 36H, $Si(CH_3)_3$), 0.00 (s, 36H, $Si(CH_3)_3$).

4.5. Thio-ether-footed trimethylsilane protected resorcin[4]arenes (10a–c)

9-BBN (17.5 ml, 8 mmol: commercial solution 0.5 M in THF) and 1-decanethiol (1.8 ml, 8 mmol) or 1-ethanethiol or 1-propanethiol were added to a solution of trimethylsilane protected resorcin-[4]arene (**9**) (3.5 g, 2 mmol) in dry THF (22 ml) cooled to −10 °C. The solution was stirred at room temperature for 16 h. After the solvent was evaporated under vacuum, the crude product was dissolved in CH_2Cl_2 (20 ml), and washed with water (3x20 ml). Next, the organic layer was dried on $MgSO_4$, filtrated, after which the solvent was evaporated under vacuum. Compounds **10a–c** were not isolated and were used further for preparing **2**, **3**, and **4**.

4.6. Thio-ether-footed resorcinarene 2

HCl 32% (4 ml) was added to the crude solution of **10a** in methanol (60 ml). The pink solution was stirred at room temperature for 16 h. The reaction was quenched with water (15 ml), and the yellow solid formed was washed with water to neutrality. After drying in vacuum at 50 °C, compound **2** was obtained in pure form after crystallization from acetonitrile (2.5 g, 72%). The total yield from the first step was 32.5%. Mp=185–192 °C, literature 222–225 °C.[20]

^{1}H NMR of hexameric **2** (400 MHz, $CDCl_3$, 25 °C, 30 mM): δ=9.61 (br s, 24H, OH), 9.37 (br s, 24H, OH), 7.19 (br s, 24H, ArH), 6.12 (br s, 24H, ArH), 4.3 (br t, 24H, ArCH), 2.49 (t, 96H, J=7.3 Hz, R–CH_2S), 2.20 (br m, 48H, ArCH–CH_2), 1.57 (m, 96H, R–CH_2–CH_2S), 1.26 (m, 672H, $(CH_2)_{14}$), 0.88 (t, 72H, J=7.1 Hz, R–CH_3).

^{13}C{^{1}H} NMR of hexameric **2** (100 MHz, $CDCl_3$, 25 °C, 30 mM): δ=150.1, 124.6, 123.0, 102.5, 42.4, 32.0, 31.8, 31.7, 29.9, 29.5, 29.4, 29.4, 29.4, 29.3, 29.3, 29.2, 29.1, 29.1, 29.1, 28.9, 28.8, 28.4, 27.9, 14.5.

MALDI MS: calculated for $C_{108}O_8S_4H_{184}$ (monomer **2**) 1737.32, found 1737.28.

4.7. Thio-ether-footed resorcinarene 3

The synthetic route for the preparation of **3** was the same as for **2**. The only difference was that propanethiol was used instead of 1-decanethiol. The yield of the last step was 83% and the overall yield was 37.8% (2.1 g). The product was obtained as an orange solid. Mp=129–132 °C.

^{1}H NMR of hexameric **3** (400 MHz, $CDCl_3$, 25 °C, 30 mM): δ=9.65 (br s, 24H, OH), 9.42 (br s, 24H, OH), 7.19 (br s, 24H, ArH), 6.12 (br s, 24H, ArH), 4.30 (br, 24H, ArCH), 2.49 (m, 96H, R–CH_2S), 2.21 (br m, 48H, ArCH–CH_2), 1.57 (m, 96H, R–CH_2–CH_2S), 1.28 (m, 336H, $(CH_2)_7$), 0.98 (t, 72H, J=7.3 Hz, R–CH_3).

^{13}C{^{1}H} NMR of monomeric **3** (100 MHz, CD_3OD, 25 °C, 30 mM): δ=151.4, 123.9, 123.1, 120.5, 41.1, 33.6, 33.1, 32.2, 31.5, 29.4, 29.4, 29.2, 29.0, 28.5, 27.7, 26.6, 22.6, 12.4.

MALDI MS: calculated for $C_{80}O_8S_4H_{128}$ (monomer **3**) 1345.04, found 1344.85.

4.8. Thio-ether-footed resorcinarene 4

The synthetic route for preparing **4** was the same as that of **2**. The only difference was that ethanethiol was used instead of 1-decanethiol. The yield of the last step was 80.6% and the overall yield was 36.5% (1.96 g). The product was obtained as an orange solid. Mp=126–130 °C.

^{1}H NMR of hexameric **4** (400 MHz, $CDCl_3$, 25 °C, 30 mM): δ=9.65 (br s, 24H, OH), 9.42 (br s, 24H, OH), 7.20 (br s, 24H, ArH), 6.12 (br s, 24H, ArH), 4.30 (br, 24H, ArCH), 2.52 (m, 96H, R–CH_2S), 2.21 (br m, 48H, ArCH–CH_2), 1.58 (m, 48H, R–CH_2–CH_2S), 1.28 (m, 336H, $(CH_2)_7$), 1.24 (t, 72H, J=7.4 Hz, R–CH_3).

^{13}C{^{1}H} NMR of monomeric **4** (100 MHz, CD_3OD, 25 °C, 30 mM): δ=151.4, 123.9, 123.1, 102.5, 41.1, 33.5, 33.0, 31.0, 29.3, 29.2, 28.5, 27.7, 26.6, 25.9, 25.2, 25.0, 13.9.

MALDI MS: calculated for $C_{76}O_8S_4H_{120}$ (monomer **4**) 1289, found 1288.78.

The stability of the capsules was studied by titrating a 3 mM solution of the macrocycles in $CDCl_3$ with CD_3OD. The samples were measured 15–20 min after the addition of methanol.

The t_e effect on the water signal decay was studied by using the LED pulse sequence with different t_es of 5 ms, 50 ms, and 150 ms. The results were then compared with the water signal decay extracted from the PGSTE diffusion sequence. Those diffusion measurements were performed on 20 mM $CDCl_3$ solutions of **2**, **3**, and **4**, and in all these solutions, the ratio between the macrocycle and water was 6:15–20.

Preparation of thiol- and thio-ether-footed resorcin[4]arenes coated gold nanoparticles was performed according to literature procedure[25] with a few modifications. Only the preparation of decanethiol-coated gold nanoparticles will be detailed. The other AuNPs were obtained through the same procedure.

4.9. Preparation of ($C_{10}H_{21}S$)·AuNPs

An aqueous solution of hydrogen tetrachloroaurate (250 mg) in 15 ml of water was mixed with a solution of tetraoctylammonium bromide (600 mg) in 50 ml of toluene. The two-phase mixture was vigorously stirred until all the tetrachloroaurate was transferred into the organic layer and then decanethiol (0.17 ml) was added to the organic phase. Next, a freshly prepared aqueous (15 ml) solution of sodium borohydride (500 mg) was slowly added with vigorous stirring and the solution turned dark brown. After further stirring for several hours, the organic phase was separated, evaporated to a 10 ml volume in a rotary evaporator, and mixed with 400 ml ethanol to remove excess thiol. The mixture was kept for several hours at −18 °C and the dark brown precipitate was centrifuged and

washed with ethanol. The crude product was dissolved in 10 ml of toluene and again precipitated with 400 ml of ethanol. Yield: 81 mg.

Using the same procedures, the yields of **2**·AuNPs, **3**·AuNPs, and **4**·AuNPs were 32 mg, 55 mg, and 89 mg, respectively.

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