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Head-to-tail Aggregates of Sulfonatomethylated Calix[4]resorcinarene in Aqueous Solutions

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Two amphiphilic water-soluble sulfonatomethylated calix[4]resorcinarene derivatives were studied by various ^{1}H NMR techniques (^{1}H NMR titration, 2D NOESY, NMR diffusion measurements). The derivative with methyl moieties at the lower rim (1) was found to be non-aggregated in the range 0–10 mM in aqueous solutions. Lengthening of the lower rim substituent to pentyl (2) results in self-aggregation of 2 in aqueous solutions with the aggregation number varying from 3 at 1 mM to 20 at 10 mM. The 2D NOESY ^{1}H NMR spectroscopy data reveal an unusual head-to-tail packing mode in aqueous solutions, resulting from the cooperative effect of weak hydrophobic interactions. Binding of guests (tetramethylammonium and N-methylpyridinium) results in additional stabilization of the aggregates whilst the head-to-tail packing mode of the aggregate is retained.

Keywords: Supramolecular chemistry; Self-aggregate; Hydrophobic interaction; NMR spectroscopy

INTRODUCTION

Amphiphilic derivatives of calixarenes are of increasing interest due to their self-aggregation in solutions, as well as their receptor properties [1–6]. Thus amphiphilic calixarenes are promising building blocks for the development of nano-scale aggregates, able to recognize molecules [7–10] and ions [11–15]. Non-covalent multiple interactions, hydrogen bonding in particular, are a well known approach for the construction of capsule-like dimers and hexamers [1,2,11–15]. Most of these systems, however, are restricted to nonpolar solvents, though there are some interesting X-ray structures of crystals grown from aqueous methanol solutions, which bring to light hydrogen bonded resorcinarene capsules with tetra-alkyl ammonium cations inside [15]. Self-assembly in polar media, e.g., aqueous medium, requires other driving forces, such as multiple electrostatic interactions [16–24] or the so-called hydrophobic effect, arising from the hydration of hydrophobic moieties of amphiphilic compounds. Amphiphilic water-soluble calix[*n*]arenes, bearing sulfonato- and ammonium groups on their rims, are known to form micellar aggregates with the critical concentrations of aggregation depending on *n*, the structure of hydrophilic groups, the length of hydrophobic moieties and conformation [25–28]. Aqueous micellar systems play a particular role in analytical chemistry and in the development of new technologies due to their ability to solubilize molecules and ions and to extract them from aqueous solutions through micellar and aqueous pseudo-phases separation. These phenomena underpin the development of ecologically non-hazardous and efficient extraction procedures [29–31]. Since amphiphilic water-soluble calix[*n*]arenes exhibit good receptor properties [1–6], calixarene-based micellar aggregates are of particular importance [11–15,25–28]. These receptor properties can be modified through self-assembly of the receptor molecules, since the conformation, as well as the pre-organization of amphiphilic groups on the rim, greatly affects complex formation and can be changed upon packing of the receptor molecules into self-aggregates. For example dimeric capsule formation results in a larger cavity than in the case of a mono-molecular receptor [1–24]. The X-ray data indicate that the nature of guest or solvents

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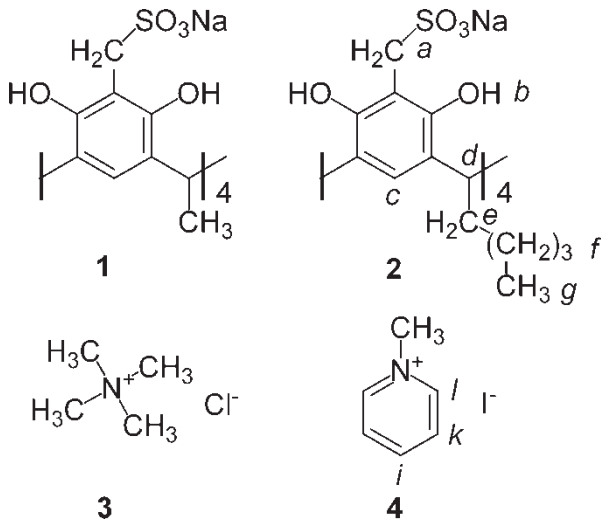

FIGURE 1 Objects of investigation.

molecules greatly affects the capsule formation [32–35]. Therefore correlations between the packing mode of self-aggregates and their receptor properties are of particular importance. There are several methods that could be used to study such systems in solution. Among them NMR methods have proved to be a powerful tool in the investigation of supramolecular systems [36–38].

This work was stimulated by previous studies of two water-soluble sulfonatomethylated calix[4]-resorcinarenes (**1** and **2**) with different length of hydrophobic moieties (Fig. 1) by the conductivity method [39]. In order to understand the main driving forces of self-aggregation in these systems we extended our studies to NMR spectroscopy investigations. Thus the work presented is devoted to the evaluation of the size and the structure of the aggregates formed in aqueous solutions at various concentrations of calix[4]resorcinarenes (**1** and **2**) itself and in the presence of guest cations (tetramethylammonium (**3**) and N-methylpyridinium (**4**)) by various NMR techniques (^{1}H NMR titration, 2D NOESY, NMR diffusion measurements).

EXPERIMENTAL SECTION

Materials

The hosts **1** and **2** were synthesized as recently reported [40]. Tetramethylammonium chloride (**3**Cl) was commercially available from "Lancaster". $CH_3NC_5H_5I$ (**4**I) was synthesized and purified as reported [41].

NMR Experiment

All NMR experiments were performed on a Bruker AVANCE-600 with pulsed gradient unit capable of producing magnetic field pulse gradients in the z-direction of about 50 G cm^{-1}. All experiments were carried out using a 5 mm diameter broadband inverse probe head at 303.0 ± 0.2 K. Chemical shifts were reported relative to HDO (4.7 ppm) as an internal standard.

The diffusion experiments were preformed at least three times and only the data, where the correlation coefficients of $\ln(I/I_0)$ versus $b = \gamma^2\delta^2 g^2(\Delta - \delta/3)$ were higher than 0.999 were included. The pulsed gradients were incremented from 0 to 32 G* cm^{-1} in 32 steps, with the duration of pulse (δ) from 1.2 ms for "free" guest molecule to 3.6 ms for the host–guest system. The pulse gradient separation (Δ) in all case was 50 ms. All separated peaks were analyzed and the average values are presented. The error of the self-diffusion coefficients determination did not exceed 5%.

It should be mentioned that the diffusion data were analyzed assuming several simplifications:

(1) The conditions of infinite dilution were assumed. Thus the dynamic viscosity of solution Eq. (1) is equal to the viscosity of pure solvent. This simplification does not introduce errors since the change in the self-diffusion coefficient of water for the samples investigated is within the experimental error (±5%) and thus insignificant. The viscosity of water $\eta(D_2O, 303\,K) = 7.98E^{-04}\,N\,s\,m^{-2}$ was used.
(2) The exchange between free and bound molecules is fast on the diffusion time scale (50 ms in our case). It can be justified by the fact, that it is already fast on the chemical shift time scale, since we observe only one set of signals in all cases. The exponential slops of signal intensity in FT-PGSE experiments also confirm this conclusion (Fig. 2).
(3) The Eqs. (1) and (2) are based on the assumption that the aggregate's shape is spherical. Since an increase in calixarene **2** concentration and the addition of guest do not change the structure of the aggregates we assume that Eq. (2) is a good approximation to evaluate the change of aggregation numbers in the systems studied. It may not be the most accurate but remains, however, the most convenient for providing a rough estimation of the size of the aggregates.

2D NOESY were performed for mixing times of 50–800 ms with pulsed filtered gradient techniques.

The pulse programs for all NMR experiments were taken from the Bruker software library.

Molecular Mechanics Calculations

Molecular mechanics (employing the MM2 force field) were performed with CS Chem3D Ultra 6.0

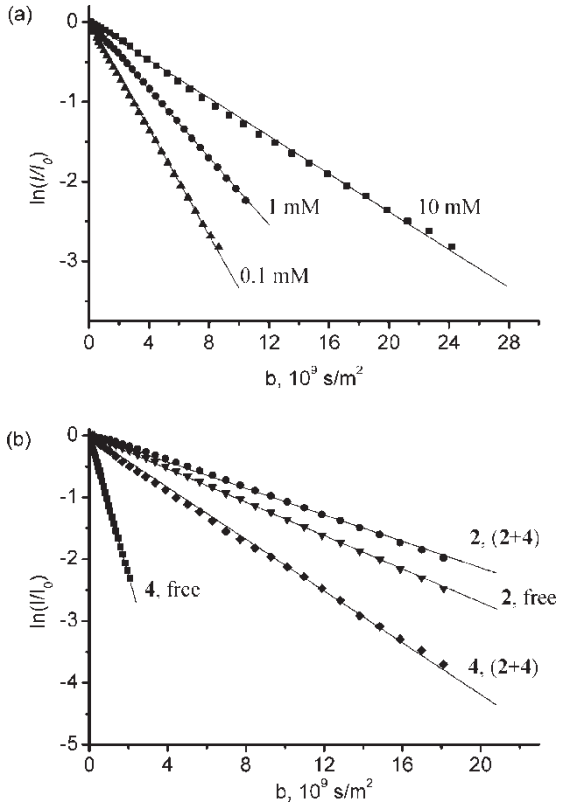

FIGURE 2 Natural logarithm of the normalized signal attenuation ln (I/I_0) of methyl groups as a function of the gradient amplitude b (a) for aqueous solutions of **2** at various concentrations: 0.1 mM (▲), 1 mM (●) and 10 mM (■); (b) for aqueous solutions of **2** (4.5 mM) (▼) and **4** (4.5 mM) (■), as well as their equimolar mixtures: signals of **2** in the presence of **4** (●), signals of **4** in the presence of **2** (◆).

(CambridgeSoft Corp http://www.camsoft.com.) on a AuthenticAMD Athlon(Im) computer.

Energy minimizations were performed with the steepest descent and adopted basis Newton–Raphson methods until the root mean square of the energy gradient was < 0.001 kcal mol^{-1} A^{-1}.

RESULTS AND DISCUSSION

The ^{1}H NMR spectra of **1** and **2** measured in DMSO at 303 K ($C = 1$ mM) possess sharp signals with one multiplet of CH-bridged protons and one singlet of the protons of the aromatic rings. This spectral pattern indicates that both resorcinarenes exist in highly symmetrical structures, which can be attributed to *rccc*- or *rtct*-isomers. The presence of cross-peaks in the 2D NOESY spectrum between the aromatic protons and the protons of the hydrophobic substituent (CH_3 for **1** and CH_2(e) for **2**) along with the absence of cross-peaks between the methylsulfonate protons and aromatic protons or of any of the aliphatic protons indicate that the investigated resorcinarenes adopt a bowl like *rccc*-conformation [42,43].

Increase of the resorcinarene **2** concentration from 0.1 to 10 mM in D_2O results in substantial broadening of signals in the NMR spectra (Table I, see Supplementary Material). The peaks of the aliphatic chains are broadened, so the splitting due to spin–spin interactions cannot be resolved at 1 mM of **2**. The signal for the aromatic protons at 10 mM is beginning to split into two signals most probably due to a more restricted boat-cone-boat inter-conversion of **2** under its association. At ambient temperature in solution boat conformers of the investigated resorcinarenes interconvert very rapidly giving a time-averaged crown structure and one set signals for all protons. The spectral pattern of the less symmetrical boat conformation can be observed in the case of the restricted interconversion. Since the boat conformation possesses two opposite phenyl rings facing each other and two rings oriented outside the cavity, the ring current effects of neighboring aromatic moieties on the aromatic protons are different. Therefore, the splitting of aromatic protons signals at 10 mM points to restricted interconversion of **2** in aqueous solutions.

So, these facts indicate a significant decrease in the mobility of **2** with increasing concentration.

The NMR Diffusion Experiment

The formation of aggregates, inferred from the NMR spectra, was confirmed by diffusion NMR experiment. The determination of self-diffusion coefficients by means of Fourier-transform pulsed gradients spin-echo (FT-PGSE) NMR [44] is known as a powerful tool for the characterization of supramolecular systems in solution [45–47]. The data presented in Fig. 2a illustrate the natural log of the normalized signal attenuation (ln I/I_0) as

TABLE I ^{1}H NMR chemical shifts (δ, ppm) and linewidth (Hz, in parenthesis) of resorcinarene **2** at various concentrations (D_2O, 303 K)

	Proton					
C, mM	*a*	*d*	*c*	*e*	*f*	*g*
0.1	4.22 (4†)	4.43 (4)	6.96 (6)	1.99 (20)	1.29 (14)	0.83 (6)
1.0	4.23 (6)	4.39 (22)	6.86 (22)	1.93 (29)	1.26 (21)	0.81 (14)
10	4.24 (12)	4.31 (22)	6.85 6.88 (25)	1.90 (31)	1.19 (26)	0.78 (14)
Δδ‡	−0.02	−0.12	−0.11	−0.09	−0.10	−0.05

† Linewidth at a half-height. The linewidth of the solvent is 2 ± 0.1 Hz in all measurements. ‡ $\Delta\delta = \delta_{[10]} - \delta_{[0.1]}$.

TABLE II The self-diffusion coefficients (D_s), hydrodynamic radius (R_H) and aggregation numbers (N_{ag}) at various concentration of calixarene **2** in D_2O

C, mM	D_s ($\times 10^{-10}$ m^2/s)	R_H (Å)	N_{ag}	D_s of HDO ($\times 10^{-10}$ m^2/s)
0.1	3.26	8,5	1	24.4
1.0	2.21	12.6	3	24.1
10	1.21	22.9	20	23.1

a function of the gradient amplitude b [$b = \gamma^2\delta^2 g^2(\Delta - \delta/3)$, where γ is the gyromagnetic ratio, g is the pulsed gradient strength, Δ is the time separation between the pulsed-gradients, δ is the duration of the pulse] at various concentrations of **2**.

The size of aggregates can be evaluated from self-diffusion coefficients according to the Stokes–Einstein equation, which shows the correlation of the hydrodynamic radius of molecule or aggregate (R_H) with self-diffusion coefficients (D_s).

$$D_s = k_B T/6\pi\eta R_H, \quad (1)$$

where k_B—Boltzmann constant, T (K)—temperature, η (Pa s)—dynamic viscosity of the solvent.

Assuming that the aggregates are spheres with radius R_H, the aggregation number can be calculated from the comparison of the aggregates volume with the volume of non-aggregated molecules according to equation.

$$N_{ag} = (R_{Ha}/R_{Hm})^3 \quad (2)$$

where R_{Hm} and R_{Ha} are hydrodynamic radii of monomer and aggregate molecules correspondingly.

The data presented in Table II illustrate the dependence of self-diffusion coefficients, and the corresponding R_H and N_{ag}-values of resorcinarene **2** on its concentration (0.1–10 mM). The R_H-value, calculated from the measurements at 0.1 mM of resorcinarene **2** (8.5 Å) agrees well with its theoretical radius, estimated on the bead model approximation [48] (8.39 Å) for the structure optimized by MM method with MM2 force field.

Thus we can conclude that at 0.1 mM in D_2O resorcinarene **2** is monomeric, while at 1 mM trimers become dominant. Further increase of concentration of **2** to 10 mM results in efficient aggregation and the aggregation number rises to ~20.

In the DMSO the hydrodynamic radius of **2** at 1 mM is close to that of its monomer 8.5 Å ($D_s = 1.37 \times 10^{-10}$ m^2/s).

Organic Cations Control the Aggregation State of 2

The addition of equimolar amounts of organic cations **3** and **4** to aqueous solutions of **2** leads to a decrease in the self-diffusion coefficients of both resorcinarene and cation (Fig. 2b). These data indicate efficient host–guest binding, leading to enhanced growth of the aggregates (Table III).

In the case of fast exchange the fraction of bound guest P_{bD} can by determined by:

$$P_{bD} = (D_{obs} - D_{free})/(D_{com} - D_{free}) \quad (3)$$

where D_{obs} is the observed (weighted average) self-diffusion coefficient of the guest molecule, D_{com} is the self-diffusion coefficient of the complex and D_{free} is that of unbound guest. In the practical application, D_{com} is not known and cannot be determined experimentally. However, since the guest has a significantly lower molecular weight, D_{com} can be assumed to be equal to D_{host} (self-diffusion coefficient of the resorcinarene), which leads to a slight overestimation of the P_{bD}-value. In our case the diffusion coefficient data indicate that even at 1:1 host–guest concentration ratio more than 90% of the guest is bound into the host–guest complex.

The self-diffusion coefficient of **1** remains unchanged within the experimental error, being equal to $D_s = 3.59{\cdot}10^{-10}$ m^2/s, when the concentration of **1** increases from 1–10 mM. The R_H-value (7.74 Å), calculated from self-diffusion coefficients agrees with that theoretically calculated on the bead model approximation R_H-value for the monomer (7.44 Å). The addition of equimolar amounts of **3** does not sufficiently affect the translation mobility of **1**. Therefore it can be concluded that resorcinarene **1** is non-aggregated within 1–10 mM in aqueous solutions, both with and without guests. The Self-diffusion coefficient of **3** in the presence of equimolar

TABLE III The self-diffusion coefficients (D_s), hydrodynamic radius (R_H) and aggregation numbers (N_{ag}) of calix[4]resorcinarenes (**1** and **2**) (4.5 mM) in aqueous solutions prior to and after addition of equimolar amounts of organic cations. The binding fractions P_{bD} of **3** and **4** (4.5 mM) in the presence of equimolar amounts of calix[4]resorcinarenes **1** and **2**

System	D_s host ($\times 10^{-10}$ m^2/s)	D_s guest ($\times 10^{-10}$ m^2/s)	R_H (Å)	N_{ag}	P_{bD}	D_s of HDO ($\times 10^{-10}$ m^2/s)
1	3.59		7.74	1		23.6
2	1.98		19.8	13		24.4
3		11.7	2.37			24.2
4		12.4	2.2			24.3
1 + **3**	3.59	9.64	7.74	1	20	23.6
1 + **4**	3.58	8.19	7.77	1	47	24.2
2 + **3**	1.03	1.95	27.0	32	91	23.4
2 + **4**	1.14	2.11	24.4	24	91	23.4

amounts of **1** decreases up to $9.64 \cdot 10^{-10}\,m^2/s$, which corresponds to $P_{bD} = 20\%$.

The Inclusion Capacity of the Aggregated Calix[4]resorcinarene

Taking into account the inclusion capacity of water-soluble calix[4]resorcinarenes towards organic cations [49,50] and that the self-diffusion data show that both resorcinarenes bind cations **3** and **4**, ^{1}H NMR spectroscopy was used to evaluate the mode of binding of cations **3** and **4** by the aggregated resorcinarene **2**. As is well known, the formation of an inclusion complex results in the up-field shift of the protons of the guest moieties included into the cavity of the cyclophanic receptor [50]. In fact, Fig. 3a indicates efficient shielding of the protons of **3** due to their inclusion into the cavity of the aggregated receptor **2**. The complexation induced shift of **3** (CIS = 2 ppm) is evident from Fig. 3a. It is natural to assume that the host–guest complex formation constant should depend on the aggregation number of the host. The analysis of the NMR titration data [50] reveals no linear dependence of $\log(\alpha/(1-\alpha))$ on $\log(C_2 - \alpha C_3)$, where C_2 and C_3 are initial concentrations of **2** and **3** correspondingly and α is the ratio of the equilibrium concentration of the bound guest and C_3, where α is calculated through the following equation: $\alpha = \Delta\delta_{obs}/CIS$ ($\Delta\delta_{obs} = \delta_{free} - \delta_{obs}$, where δ_{free} and δ_{obs} are the chemical shifts of the guest prior and after addition of various amounts of host). This is in accordance with the aggregation number of the host being varied within the usable concentration range. Nevertheless the α-value is within 90–95%, when the concentration host:guest ratio is close to 1:1, thus indicating that the aggregated **2** is a more efficient receptor than the monomeric **1** (α is within 10–15% at the same concentration conditions [49]).

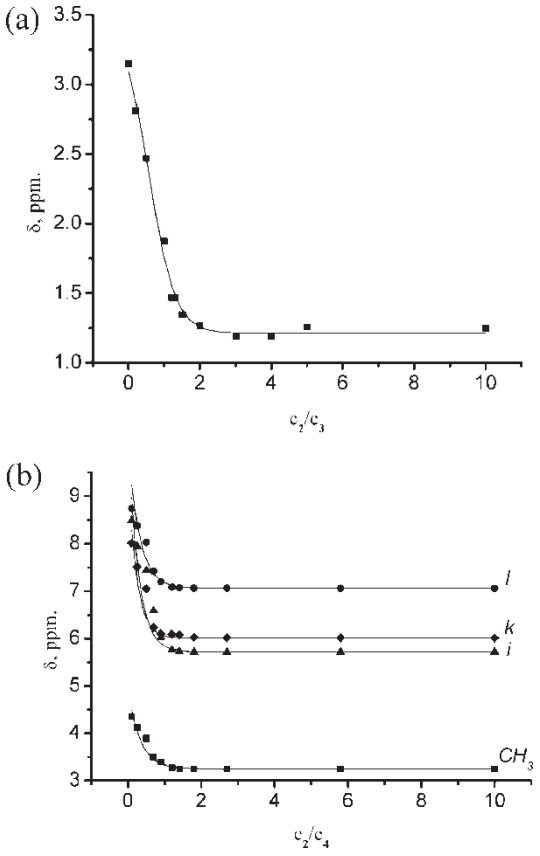

FIGURE 3 Chemical shifts of N–Me protons of guests **3** (a) and **4** (b) versus host/guest concentration ratio, where host is **2**.

Figure 3b illustrates the chemical shifts change of guest **4** protons under its binding with the aggregated resorcinarene **2**. Similar analysis as in the case of guest **3** also reveals that 1:1 binding is not valid for **4** within the whole range of the concentrations studied. The non-symmetrical structure of **4** is a premise of its bilateral inclusion into the cavity of receptor via both methyl and aromatic moieties. The data presented in Table IV comprise CIS-values of **4** under its binding with calixarenes **1** and **2**.

As one can see from Table IV the binding of **4** with both resorcinarenes leads to an up-field shift of aromatic and methyl protons signals of **4**, indicating that the bilateral guest is included into the cavities of receptors via both N-methyl and aromatic moieties. The up-field shift of CH_i proton signals of **4** is more pronounced on binding with **2** than with **1**. At the same time the up-field shifts for CH_l and CH_3 protons are apparently less on binding with **2** than with **1**. Thus the comparison of the up-field shifts exhibited by $N{-}CH_3$ and aromatic protons on binding with both resorcinarenes reveals that the inclusion of **4** into the cavity of the aggregated resorcinarene **2** occurs predominantly via its aromatic moiety, while the inclusion into the monomeric **1** occurs to be less selective. The literature data [51–53] reveal that the predominant binding mode of bilateral organic cations by water-soluble calixarenes is driven by the interplay of the two main contributions: electrostatic and CH–π or π–π interactions. Thus the data obtained indicate that the latter contribution becomes more important for the aggregated receptor **2** than for its monomeric analogue **1**.

In the framework of the 1:1 approximation, the α-value, evaluated from the NMR titration data for **2** is within 90–95%, when the concentration ratio is

TABLE IV Complexation induced shifts (CIS, in ppm) of guest **4** on binding with monomeric (**1**) and aggregated (**2**) hosts

Host	CH_3	CH_l	CH_k	CH_i
1	−1.28	−2.82	−2.57	−2.18
2	−1.11	−1.68	−2.0	−2.78

close to 1:1 for both cations. These data are in satisfactory agreement with the above mentioned value (~90%), derived from diffusion data with equimolar amounts of host and guest. It is worth noting that inclusion complex formation is not the only mode of binding between resorcinarene anions and counter ions **3** and **4**. In particular electrostatic interactions of both counter ions with sulfonate groups are also probable. Such binding will provide an insignificant effect on the chemical shifts of **3** and **4**, but a significant effect on the self-diffusion coefficient. Therefore the good agreement between the NMR titration and diffusion data indicates that the inclusion-type complex formation is predominant at the equimolar amounts of host and guest.

The Structure of Self-aggregates

The shift of resonance peaks, induced by the ring current of the aromatic fragments, is one of the NMR tools, which enables the determination of the structure of resorcinarenes complexes [54]. In our case the change of chemical shifts of protons for all groups with increase in the concentration of **2** are not pronounced (less than 0.1 ppm). Moreover, the degree of the broadening of aliphatic chains peaks are nearly the same for all groups (*e*, *f*, *g*; Table I). These data do not evaluate the mutual arrangement of neighboring molecules, but do allow the exclusion of the presence of different binding modes in the self-aggregates.

The ^{1}H 2D-NOESY spectra of **2** in D_2O were performed at the mixing times from 50 to 800 ms in order to minimize the errors, caused by probable spin-diffusion. Even at a short mixing time the cross peaks between $\underline{CH_2}S$ and aliphatic protons from the lower rim are observed in NOESY spectra (Fig. 4). Due to the slow molecular motion of this compound the sample is in a negative NOE regime and negative NOE enhancement are observed. Taking into account that in the cone conformation the distance from $\underline{CH_2}S$ to aliphatic protons is ca. 6–9 Å the cross peaks in 2D-NOESY spectra can be attributed only to intermolecular NOE. To support this conclusion additional 2D NOESY experiments with **2** in a more viscous solvent (DMSO) were carried out and indeed no such cross peaks were observed. Since calixresorcinarene **2** does not exhibit significant change of conformation on going from aqueous to DMSO solutions, the intramolecular distances between the protons of various functional groups should be nearly the same in both solutions. Taking into account that resorcinarene **2** is in the aggregated form in aqueous and is non-aggregated in DMSO solutions (look the diffusion data), the disappearance of NOEs cross peaks after changing aqueous to DMSO solutions points to the intermolecular origin of the NOE in D_2O.

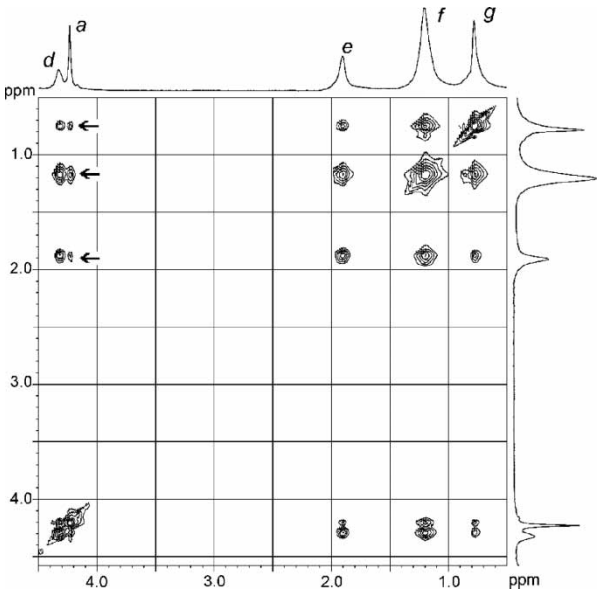

FIGURE 4 Part of the 2D NOESY NMR spectrum of **2** at 4.5 mM in D_2O, 303 K, mixing time of 200 ms. The NOE observed between protons of methylsulfonate and aliphatic groups are indicated by arrows.

The only plausible explanation for these observations is the head-to-tail packing mode of self-aggregates. The structural unit in this case contains two resorcinarene molecules, where the aliphatic chains of one resorcinarene (lying above) are close to methylsulfonate groups of the neighboring one (lying below), while the insertion of aliphatic chains into the cavity of the molecule lying below does not occur.

The guest molecules can serve as probes for additional justification of the packing mode. Indeed, the diffusion data show that the guest molecules in equimolar mixtures with the aggregated calixarene **2** were efficiently bound (<90%) and inserted into the cavities (CIS = 2 ppm). Therefore, the cross peaks between guest protons (**3** or **4**) with both methylsulfonate protons and protons of aliphatic chain observed in NOESY spectra (Fig. 5) point to a head-to-tail packing mode when the bound guest molecule is clamped between the alkyl chains of the calixarene molecule lying above and the cavity of the neighboring one (lying below) (Fig. 6).

Keeping in mind that the hydrophobicity of the lower rim substituents (pentyl for **2** and methyl for **1**) is the main difference between the aggregated **2** and monomeric **1**, it is reasonable to suggest that the hydrophobic effect is of vital importance in self-aggregation of **2**. Therefore the fast exchange in NMR time scale observed in aqueous solutions of the aggregated **2** is quite different from calixarene-based capsules in nonpolar solvents with slow exchange [7–24], since the hydrophobic forces are less efficient and rigid than the intermolecular hydrogen bonding. The sulfonate groups on the upper rims of

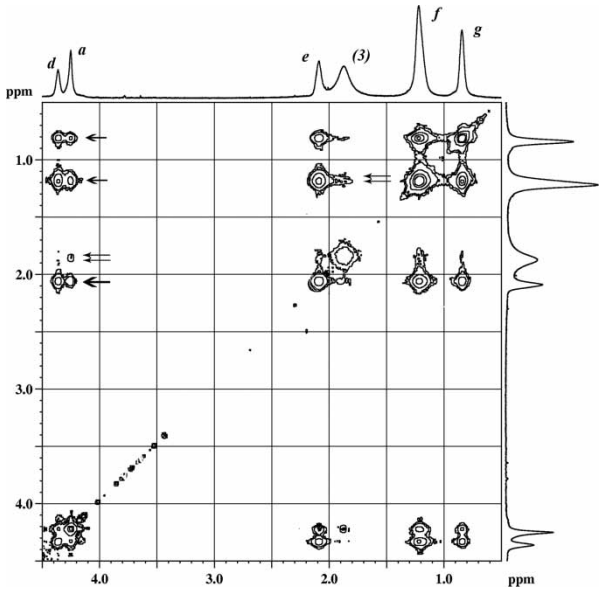

FIGURE 5 Part of the 2D NOESY NMR spectrum of equmolar mixture **2** and **3** at 4.5 mM in D_2O, 303 K, mixing time of 200 ms. The NOE observed between protons of methylsulfonate and protons of aliphatic groups of **2** are indicated by arrows. The NOE observed between protons of **2** and protons of guest **3** are indicated by double arrows.

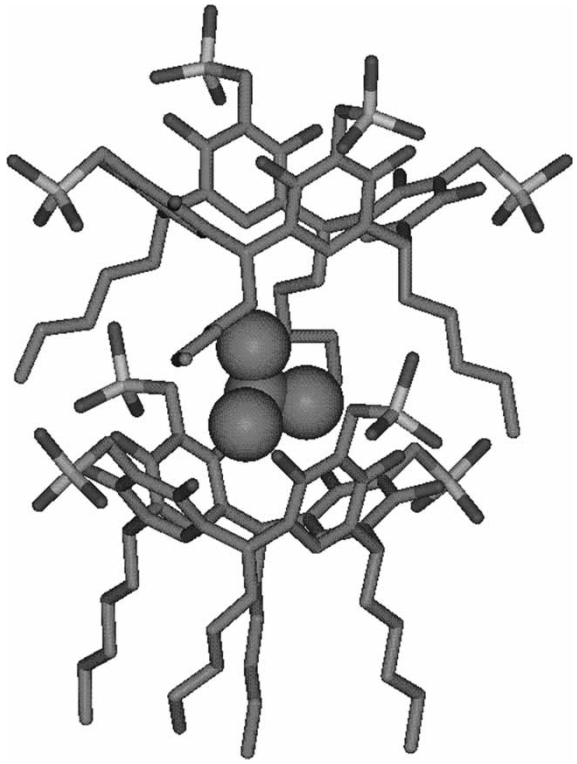

FIGURE 6 Stick model of the proposed structure of the subunit of the aggregated resorcinarene **2** + $N^+(Me)_4$ (**3**). The guest molecule is represented as a space filling model. The gas phase minimized structure.

resorcinarenes **2** possess conformational flexibility due to the presence of methylene bridges, which serve as spacers between sulfonato groups and the resorcinarene matrix. The conformation flexibility provides the orientation of sulfonate groups out of the cavity. Therefore pentyl moieties of one resorcinarene (lying above) can be arranged between sulfonatemethyl groups of the neighboring one (lying below). In such a case pentyl moieties are in close proximity to methylene bridges of methylsulfonate groups, while sulfonate groups are oriented out of cavity, developing thus the hydrophilic surface of the aggregates. This head-to-tail structure results in the decrease of both the hydrophobic surface of the aggregates and the electrostatic repulsion of the sulfonate groups.

It is also worth noting that the presence of four negatively charged sulfonatomethyl groups on each resorcinare molecule provides an excess negative charge in their aggregates, which can be partly compensated by the binding with counter-ions. Thus the enhancement of the aggregation resulting from the binding with counter-ions **3** and **4** is similar with aggregates growth induced by counter ion effect, peculiar for ionic micelles [50]. In the case of **3** the aggregates growth is more than for **4**, indicating that though the electrostatic contribution is an important driving force of the binding of guests **3** and **4** with the aggregated receptor **2**, it is not major due to the cooperative multifold hydrophobic interactions which arise, when the guest is inserted into the capsule like subunit, consisting of two neighboring molecules of **2**.

CONCLUSIONS

Increasing the length of the hydrophobic part of the alkyl substituent of sulfonatomethylated calix[4]-resorcinarenes from methyl (**1**) to pentyl (**2**) leads to an apparent difference in aggregation and receptor properties towards organic cations in aqueous solutions. Keeping in mind that calixarene **2** is more hydrophobic than **1**, the difference in their aggregation capacity reveals that the hydrophobic effect plays an important role in the self-aggregation of **2**. Since the hydrophobic forces, which are responsible for the self-aggregation in aqueous media, are less efficient and rigid than intermolecular hydrogen bonding in non-polar solvents, the capsule-like subunit of the aggregate in aqueous solution is kinetically labile. Nevertheless the head-to-tail binding mode of aggregate is dominant. Binding of the negatively charged aggregated resorcinarene **2** with organic cations results in an increase in the aggregation number due to additional stabilization of the aggregates. The stabilizing effect was found to be different for the similar charged tetramethylammonium and N-methylpyridinium,

indicating that the shape of the guest along with the charge compensation effect plays a role in the stabilization of the three-dimensional structure of the aggregates.

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