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Guest controlled aggregation of amphiphilic sulfonatomethylated calix[4]resorcinarenes in aqueous solutions

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ABSTRACT

Supramolecular nanoaggregates formed through the association of amphiphilic sulfonatomethylated calix[4]resorcinarenes with different substituents on the lower rim (methyl, pentyl, heptyl) and number of aromatic, aliphatic, and cationic guests differing in their shapes and sizes were investigated in aqueous solution by various NMR techniques (^{1}H, 2D NOESY, FT-PGSE). It was shown that slight variations of the alkyl chain length on the lower rim of calixresorcinarenes dramatically change their aggregation behavior. Unlike the other calixresorcinarenes studied, the “head-to-tail” packing mode is observed for calixresorcinarene with pentyl moieties on the lower rim, which is unusual for amphiphilic calixarene aggregates. This calixresorcinarene demonstrates the stronger binding capacity toward the guest molecules due to their encapsulation into the capsule-like aggregate subunits. The guest–host complexation modifies the properties of both components, with the size of the resulted colloid particles being controlled by the guest nature.

1. Introduction

At present, the importance of surfactants in practice continues to grow. They are used in antibacterial compositions, liquid crystals, oil recovery, mineral flotation, and other fields of material science [1–4]. Current investigations in surfactant science are motivated by the requirements for designing of surfactants that possess enhanced physicochemical properties and are applicable in complex systems and in modern technologies [4–6]. The way to attain these goals is the proper design of corresponding amphiphilic building blocks, since the packing mode determining their specific aggregate morphology must be encoded in their molecular architecture. Therefore, the controllable self-assembly of specific amphiphilic molecules leading to the precisely defined and stable micelles is a challenging task from both fundamental and practical viewpoints [1,5]. Taking this into account, amphiphilic calixarene may be considered as a very promising platform, which is supported by the following considerations.

For typical surfactants, regularities of their aggregation in aqueous solutions are well documented and understood [1,5,7]. Meanwhile, these regularities may not be valid for biological and pharmacological polyaromatic compounds with indistinctly separated hydrophilic and lipophilic molecular fragments [8,9]. Due to their intermediate structural behavior, amphiphilic cyclophanes can be successfully used for modeling and better understanding of the aggregation behavior of biorelevant amphiphiles.

The specific aggregation mode of cyclophane based amphiphiles is quite different from that of conventional surfactants, and therefore, calixarenes may be successfully used for the enlargement of morphologies of amphiphilic assemblies and modification of their properties. Calixarenes are versatile macrocyclic compounds composed of a hydrophobic core sandwiched between two functionalizable rims [10,11]. Because of their facile modification [10–12], calixarenes are particularly attractive for the construction of “surfactants with a host–guest recognition site” [13]. Shinkai et al. showed that p-sulfonatocalixarenes bearing appropriate alkyl groups at the lower rim form micelles in aqueous solution [13]. They also demonstrated that the conformation of the calixarene is a crucial parameter in modulating the aggregation behavior [14], and the cone conformation of calixarene is ideal for the formation of globular micelles. After Shinkai’s pioneering work, several examples of amphiphilic calixarenes were published [15–24]. Strobel et al. [25] showed that the nature of the ionic head group is another key parameter controlling the aggregation behavior of calixarene amphiphiles, for example, carboxylated calixarenes form vesicles, whereas calixarenes with trimethylammonium head groups form micelles. Hirsch’s group [26] used calix[4]arene as a building block to construct an amphiphile that assembled into completely uniform and structurally precise micelles, which are spontaneously formed by exactly seven monomers in aqueous solution and are not deformed upon drying.

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In contrast to conventional surfactants, amphiphilic calixarene can form stoichiometric host–guest complexes between macrocyclic hosts and appropriate guest molecule. The formation of these complexes is based on non-covalent interactions and provides an approach to modulate the physicochemical properties of both the guest molecules and calixarenes or their aggregates. The complexation with calixarene can result in beneficial modification of guest molecules such as enhancement in solubility, stabilization of labile guests, physical isolation of incompatible compounds, and control of volatility and sublimation. Furthermore, the chemical reactivity of the guest is often changed by the incorporation into the cavity [27–29]. The formation of the host–guest inclusion complexes may affect the geometry of the self-assembled structures [30,31]. Houmadi and coworkers described a calix[6]arene-based system that can produce self-assemblies under the control of pH or of a metal ion due to the introduction of imidazole functional groups. Interestingly, the assemblies are constituted of hydrophobic pockets that have been shown to be capable of hosting a variety of neutral molecules as a monomer [32]. Calixarenes and resorcinarenes can be utilized as building blocks for true supramolecular amphiphiles, in which the hydrophobic and hydrophilic parts of the supramolecule are linked through weak force interactions [33,34]. Yu et al. [33] demonstrated that a hydrophilic calix[4]arene–PEG conjugate forms an inclusion complex with hydrophobic phenyl palmitate (guest), which further assembles in water into vesicles, micelles, or network-like structure. The elegance of this system lies in the simple way of controlling the equilibrium between each species by changing the ratio of hydrophobic and hydrophilic counterparts in the system. An increase in the amount of hydrophobic guest changes the equilibrium from vesicles with a diameter of 270 nm to micellar species with a diameter of 130 nm at the 1:1 ratio, and finally, the excess of guest leads to the formation of network aggregates.

These studies highlight the versatility of systems based on amphiphilic calixarenes. Nevertheless, there are only very few investigations devoted to the packing modes of self-assemblies of amphiphilic calixarenes in solutions. Besides, lack of information occurs on the interdependence of guest and host upon the self-organization.

We have recently shown that sulfonatomethylated calix[4]resorcinarene with pentyl moieties at the lower rim (**H2**) self-assembles in aqueous solutions at the concentration of $\geqslant 1$ mM with an unusual "head-to-tail" packing mode. The binding of guest molecules (tetramethylammonium or N-methylpyridinium cations), that is, the inclusion of the guest into the complex, increases the aggregation number with the retention of the "head-to-tail" packing of calix[4]resorcinarene molecules [35]. These findings encouraged us to proceed with the study of the possibility of control of the aggregation behavior of amphiphilic calixarenes by means of host–guest interactions. Here, we present the results of the NMR study of the influence of the guest molecule structure on the binding properties, size, and structure of the aggregates formed by calix[4]resorcinarenes (**H1**–**H3**) with various lengths of hydrophobic substituents. As guests, biologically active compounds dimephosphon (**G1**) and xymedon (**G2**); neurotransmitters theophylline (**G3**), tyramine (**G4**), and choline (**G5**); aliphatic cations tetramethylammonium bromide (**G6**) and tetrabutylammonium chloride (**G7**); and aromatic ammonium cations 1-methyl-4,4′-bipyridinium phosphorus hexafluoride (**G8**) and methylviologen (**G9**) were explored. By variety of aromatic, aliphatic, and cationic guests, we tried to diversify the most important physico-chemical properties of guest molecule, that is, polarities, sizes, shapes, symmetry, and the charge character. The influence of solvent on the aggregation processes in these systems is also considered.

Thus, the paper focuses on two main features responsible for the application of amphiphiles, namely their capacity for controllable self-assembling and guest–host interacting. The data obtained would contribute to the fundamentals of the aggregation behavior and receptor ability of the organized systems at the molecular level, since NMR spectroscopy, especially pulse field gradient sequences, is a powerful tool making it possible to meet a lack of knowledge on the structural behavior of both guest and host upon their self-assembling [36–40].

2. Materials and methods

2.1. Materials

2,8,14,20-Tetramethyl-4,6,10,12,16,18,22,24-octahydroxy-5,11,17,23-tetrakissulfonatomethylen calix[4]arene tetrasodium salt (**H1**), 2,8,14,20-tetrapentyl-4,6,10,12,16,18,22,24-octahydroxy-5,11,17,23-tetrakissulfonatomethylen calix[4]arene tetrasodium salt (**H2**) and 2,8,14,20-tetraheptyl-4,6,10,12,16,18,22,24-octahydroxy-5,11,17,23-tetrakissulfonatomethylen calix[4]arene tetrasodium salt (**H3**) were synthesized as reported [41]. O,O-dimethyl-1,1-dimethyl-3-oxobutylphosphonate (Dimephosphon®) (**G1**) and 1,2-Dihydro-4,6-dimethyl-N(β-oxyethyl)-2-oxopyrimidine (Xymedon®) (**G2**) were kindly provided by Prof. V.S. Reznik and Dr. A.A. Muslinkin, 1,3-dimethyl-7H-purine-2,6-dione (theophylline monohydrate) (**G3**), 4-(2-aminoethyl)phenol (tyramine) (**G4**), 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium chloride (choline) (**G5**), tetra-*n*-butylammonium chloride (**G7**), tetramethylammonium bromide (**G6**) and sodium dithionite ($Na_2S_2O_4$) are commercially available and were used without further purification. 1-Methyl-4,4′-bipyridinium phosphorus hexafluoride (**G8**) was synthesized as reported [42]. 1,1′-Dimethyl-4,4′-bipyridinium phosphorus hexafluoride (methylviologen) (**G9**) was synthesized as reported [43].

2.2. NMR experiments

All NMR experiments were performed on a Bruker AVANCE-600 spectrometer. The spectrometer was equipped with a Bruker multinuclear z-gradient inverse probe head capable of producing gradients with strength of 50 G cm^{-1}. All experiments were carried out at 303 ± 0.2 K. Chemical shifts (CSs) were reported relative to HDO (4.7 ppm) as an internal standard. The Fourier transform pulsed-gradient spin-echo (FT-PGSE) experiments [38–40,44] were performed by BPP–STE–LED (bipolar pulse pair–stimulated echo–longitudinal eddy current delay) sequence [45]. Data were acquired with a 50.0 ms diffusion delay, with bipolar gradient pulse duration from 2.2 to 6.0 ms (depending on the system under investigation), 1.1 ms spoil gradient pulse (30%), and a 5.0 ms eddy current delay. The bipolar pulse gradient strength was varied incrementally from 0.01 to 0.32 T/m in 16 steps. The temperature was set and controlled at 303 K with a 535 l/h airflow rate in order to avoid any temperature fluctuations owing to sample heating during the magnetic field pulse gradients.

After Fourier transformation and baseline correction, the diffusion dimension was processed with the Bruker Xwinnmr software package (version 3.5). The diffusion constants were calculated by exponential fitting of the data belonging to individual columns of the pseudo 2D matrix. Single components have been assumed for the fitting routine. The diffusion experiments were performed at least three times, and only the data with the correlation coefficients of a natural logarithm of the normalized signal attenuation ($\ln I/I_0$) as a function of the gradient amplitude $b = \gamma^2\delta^2g^2(\Delta - \delta/3)$ (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) higher than 0.999 were included. All separated peaks were analyzed, and the average values were