

New Insights into the Interactions between Dendrimers and Surfactants by Two Dimensional NOE NMR Spectroscopy

Yiyun Cheng,^{*,†} Yiwen Li,[†] Qinglin Wu,[‡] and Tongwen Xu^{*,†}

Laboratory of Functional Membranes, Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, People's Republic of China and Hefei National Laboratory for Physical Sciences at Microscale and School of Life Sciences, University of Science & Technology of China, Hefei, Anhui 230027, People's Republic of China

Received: June 5, 2008; Revised Manuscript Received: July 15, 2008

The interactions between polyamidoamine dendrimers and different surfactants including sodium dodecyl sulfate (SDS) and dodecyltrimethyl ammonium bromide in aqueous solutions have been investigated by a NOESY NMR technique. Strong NOE cross-peaks between hydrophobic chain protons of SDS and methylene protons of cationic dendrimers were found, suggesting a strong tendency for the long hydrophobic tails of SDS to associate with the hydrophobic pockets of dendrimers. The hydrophilic head of SDS localizes near the core or the boundary of each generation of dendrimers, and the hydrophobic chain of SDS localizes in the relative nonpolar pockets of dendrimers. The encapsulation of surfactant monomers by dendrimers is dependent on the charge type of the surfactants, the surface functionality, and the generation of dendrimers. The NOESY analysis provides a new insight into interactions between dendrimers and surfactants in comparison with previous investigations.

Introduction

Dendrimers are a class of artificial macromolecules that have a topological structure like a tree.^{1,2} They are hyperbranched, monodisperse, three-dimensional molecules with well-defined shapes, molecular weights, sizes, branched layers, hydrophobic pockets, and surface functionalities.^{1,3} Generally, dendrimers consist of three distinct components: (1) a central core from which the construction of dendrimers initiates or ends; (2) repeated branches covalently attached to the initiator core and organized in a series of radically concentric layers called “generations”; and (3) large numbers of terminal functionalities located on the surface of the macromolecules.^{1,4} They are able to encapsulate small lipophilic molecules into their relative nonpolar cavities by hydrophobic interactions, or to bind oppositely charged molecules on their surface by electrostatic interactions.^{5–7} The host ability of dendrimers toward a wide range of guests has received a great deal of attention over the past decade.^{8–10}

Ionic surfactants with amphiphilic properties make ideal guests for dendrimers because of their long hydrophobic tails and the negatively or positively charged heads in their structures.¹¹ The formation of different kinds of dendrimer–surfactant complexes was reported in previous studies.^{12–15} The structure, nature, and interaction mechanisms of these complexes are of interest because of their importance in many fields, such as the transport of dendrimers across cell membranes, the biomimicry of many biological systems, isolation of membrane-proteins, pharmaceutical sciences, and enhanced oil and mineral recovery.¹¹ Until now, the interactions of dendrimers with surfactants have been studied in detail by using various techniques, such

as fluorescence probe,^{11,14–20} isothermal titration calorimeter (ITC),¹² electron paramagnetic resonance (EPR),^{13,21,22} Krafft temperature,^{23–26} viscosity,^{26,27} surface tension,^{17–20,26} SDS-specific electrode,¹² solution turbidity,^{14,19,28} atom force microscopy (AFM),^{14,23} transmission electron microscopy (TEM),¹⁴ dynamic light scattering (DLS),^{17,19,26} small angle neutron scattering (SANS),¹² electrical conductivity,^{19,20,23,26,28} and ¹H NMR.^{22,28} In an early study, Turro and Tomalia pointed out that carboxyl-terminated dendrimers form two types of dendrimer-templated surfactant aggregates (noncooperative and cooperative) with a cationic surfactant (dodecyltrimethyl ammonium bromide, DTAB) by a fluorescence probe method.^{11,16} Later, they analyzed the aggregation process of surfactants in the presence of dendrimers by EPR spectroscopic studies.^{13,21} Different types of aggregate structures, depending on dendrimer/surfactant concentration, dendrimer generation, and system temperature were proposed. Esumi et al. also suggested the formation of large aggregates after the addition of sodium dodecyl sulfate (SDS) monomers into quaternized dendrimer (modified with hydrophobic chains or sugars) or carboxyl-terminated dendrimer solutions, based on surface tension and fluorescence probe studies.^{17–20} Bakshi et al. further supported the self-aggregation of surfactants on the surface of dendrimers by fluorescence probe, Krafft temperature, viscosity, AFM, and electrical conductivity measurements.^{14,15,22–28} More recently, Holzwarth and Wyn-Jones investigated the interactions between dendrimers and different kinds of surfactants by SDS-specific electrode, ITC, and SANS analysis.¹² Although a lot of research has been done on such interactions, all of these interactions were proposed on the surface of dendrimers and nothing is known about interactions of the hydrophobic pockets of dendrimers with the long hydrophobic tails of surfactants.

Here, we use the two-dimensional nuclear Overhauser effect spectroscopy (2D-NOESY) NMR technique to characterize the details of the encapsulation of surfactants inside poly(amidoamine) (PAMAM) dendrimers and to provide new insight into the

* To whom correspondence should be addressed. E-mail: yycheng@mail.ustc.edu.cn; twxu@ustc.edu.cn.

[†] Laboratory of Functional Membranes, Department of Chemistry, University of Science and Technology of China.

[‡] Hefei National Laboratory for Physical Sciences at Microscale and School of Life Sciences, University of Science & Technology of China.

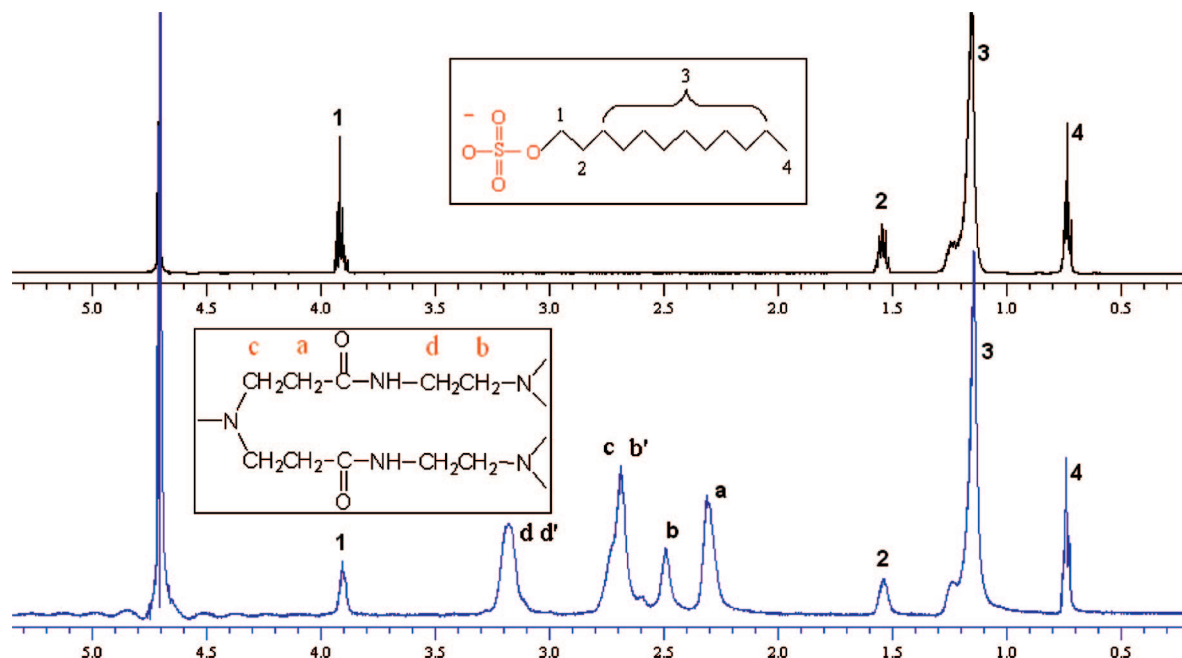


Figure 1. ¹H NMR and assignments of proton chemical shifts for SDS and its complex with G5 PAMAM dendrimer in D₂O, a~d represents the scaffold protons of dendrimer and 1~4 denotes the hydrophobic chain protons of SDS.

interactions between the two species in comparison with previous studies. PAMAM dendrimers were chosen for this study because they are the first synthesized, well-characterized, and the most widely used dendrimers. In this study, different generations of PAMAM dendrimers involving generation 3 (G3), G5, G4.5, and G6 and different types of surfactants involving anionic surfactant-SDS and cationic surfactant-DTAB were employed. All of the PAMAM dendrimers used in this study have an ethylenediamine (EDA) core. For full generation PAMAM dendrimers (G3, G5, G6), the surface functional groups are primary amine groups, whereas the surface functional groups are carboxylate groups for half-generation dendrimers (G4.5). These dendrimers have excellent solubility in aqueous solutions. The molecular formula, molecular weight, numbers of amine groups and repeated units, and the density of surface function groups are available in Table S1 in the Supporting Information. Both SDS and DTAB have a long hydrophobic tail (12 carbon atoms) and a hydrophilic head (sulfate for SDS and quaternary ammonium for DTAB).

Experimental Section

Materials. G3, G5, and G6 EDA-cored and amine-terminated PAMAM dendrimers, and G4.5 EDA-cored and carboxylate-terminated PAMAM dendrimer were purchased from Dendritech, Inc. (Midland, MI). SDS and DTAB were obtained from Shanghai BBI Co. Ltd. (Shanghai, China). Deuterium oxide (D₂O) was purchased from Beijing Chongxi High-Tech Incubator Co., Ltd. (Beijing, China). The PAMAM dendrimers stored in methanol solutions were distilled to remove the solvents before the NMR studies. Other chemicals were used as received.

NMR Measurements. All 500 MHz proton NMR spectra of D₂O solutions were obtained with a 500.132 MHz NMR spectrometer (Bruker, German) at 298.2 ± 0.1 K. 2D-NOESY spectra for the solutions of PAMAM dendrimers and surfactants (the components of these NOESY samples are listed in Table S2 in the Supporting Information) were performed with standard pulse sequences. The experimental data, consisting of 8 transients, were collected over 2048 complex points. A mixing

time of 100, 300, or 500 ms, a relaxation delay of 2 s, an acquisition time of 205 ms, and a 90° pulse width of 8.2 μs were used. The data were processed with a Lorentz-to-Gauss window function and zero filling in both dimensions to display data on a 2048 × 2048 2D-matrix. All data were processed with NMRPipe software on a Linux workstation. The NOE intensities were calculated with Sparky software.

Results and Discussion

The ¹H NMR spectra of the dendrimer/SDS/D₂O mixture shown in Figure 1 have two groups of peaks, corresponding to the proton signals from SDS chain and dendrimer scaffold, respectively. For the SDS molecule, there are four kinds of peaks assigned as 1~4. The methylene group next to the hydrophilic head of SDS is 1, the neighboring methylene group is 2, the terminal methyl group is 4, and the nine remaining methylene groups are 3. For the dendrimer molecule, the ¹H NMR spectra should have six ¹H peaks corresponding to the four CH₂ protons in the interior of dendrimer (a, b, c, and d) and two CH₂ protons in the outermost layer of dendrimer (b' and d'). However, the peaks for protons (d) and (d') are overlapped for G5 dendrimer in aqueous solutions at pH ≈ 10, and the chemical shift of protons (b') is similar to that of protons (c). Therefore, only four broad ¹H peaks can be found in the ¹H NMR spectrum of dendrimers. The labeling of protons in the repeated unit of dendrimer and SDS molecule is shown in Figure 1. Compared with the pure SDS solution, there is not much of a shift (slightly broaden) in protons (1~4) of SDS when G5 PAMAM dendrimer is present.

2D-NOESY experiments were made to determine the dipolar contacts for both intermolecular and intramolecular interactions between dendrimers and surfactants. The NOESY analysis is capable of revealing spatial relationships among protons in a molecule or in a complex of molecules. The intensity (volume) of cross-peak between two specific protons in NOESY spectra predominantly depends on the proton distance. If there is a NOE interaction between protons of host and guest, then a cross-peak should be seen in corresponding spectral region. In other

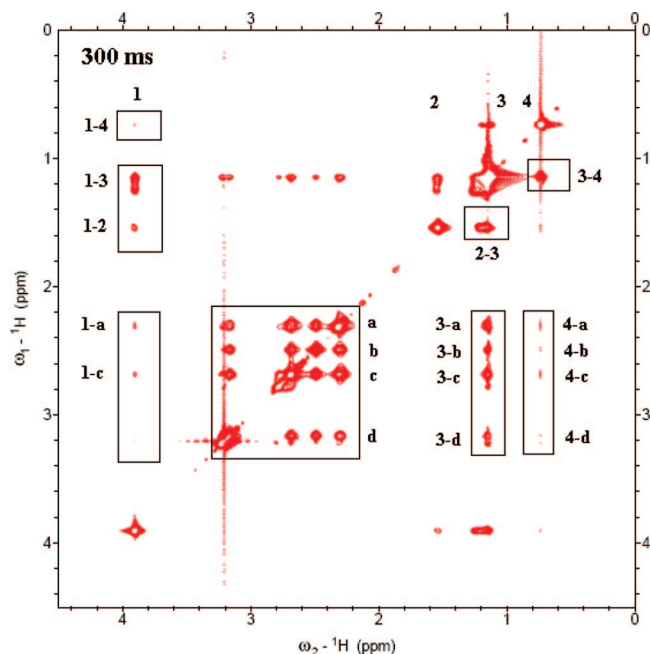


Figure 2. 2D-NOESY spectra of G5/SDS/D₂O solution (2 mg dendrimer in 1 mL D₂O, dendrimer/SDS mass ratio = 1) at mixing time of 300 ms.

words, the absence of a cross-peak in the region can be used to rule out the interaction between related protons. The NOESY spectra of G5/SDS/D₂O mixture (2 mg G5 dendrimer, dendrimer/SDS mass ratio is 1, dissolved in 1 mL D₂O) at different mixing times are shown in Figure 2. Strong positive NOE cross-peaks between the hydrophobic chain protons (**1**, **3**, and **4**, δ_{H} 3.91 for **1**, δ_{H} 1.06–1.24 for **3**, and δ_{H} 0.74 for **4**, respectively) of the SDS and pocket protons (**a**, **b**, **c**, and **d**, chemical shifts of **a**, **b**, **c**, and **d** are 2.32, 2.49, 2.69, and 3.17, respectively) of G5 PAMAM dendrimer are observed. Generally, the presence of NOE cross-peak between two protons at a sufficiently short mixing time means the protons are close within a distance of 5 Å. However, spin diffusion (indirect magnetization transfer) occurring at long mixing times can give rise to pseudo cross-peaks and thereby cause inaccurate conclusions on the spatial distance between protons.²⁹ In order to exclude the contributions of spin diffusion to the cross-peaks in the NOESY spectra, the NOESY experiments of G5/SDS/D₂O were conducted at different mixing times ranging from 100 to 500 ms (Figure 2 and Figure S1 in the Supporting Information). The cross-peak intensities of G5 (**a**–**d**)/SDS (**1**, **3**, and **4**) increase in an approximately linear manner with increasing mixing times (Figure 3), suggesting that these cross-peaks are mostly ascribed to primary NOE interactions²⁹ at a mixing time lower than 500 ms (300 ms was selected as the mixing time for other NOESY studies). These results demonstrate the spatial proximity of the hydrophobic chain protons (**1**, **3**, and **4**) of anionic surfactant SDS and the methylene protons (**a**–**d**) of G5 dendrimer.

For PAMAM dendrimers, the hydrophobic region of dendrimers is the relatively nonpolar pockets inside dendrimers consisting of ethylene groups and amide groups (Figure 1), whereas the hydrophilic region is composed of the surface functional groups (primary amine groups or carboxylate groups). The ethylene groups in the hydrophobic region of dendrimers can interact with lipophilic guests (hydrophobic chains of SDS or DTAB) by hydrophobic interactions. The amine groups in the pocket of PAMAM dendrimers can act as hydrogen-bond donors and interact with hydrogen-bond receptors (sulfate groups

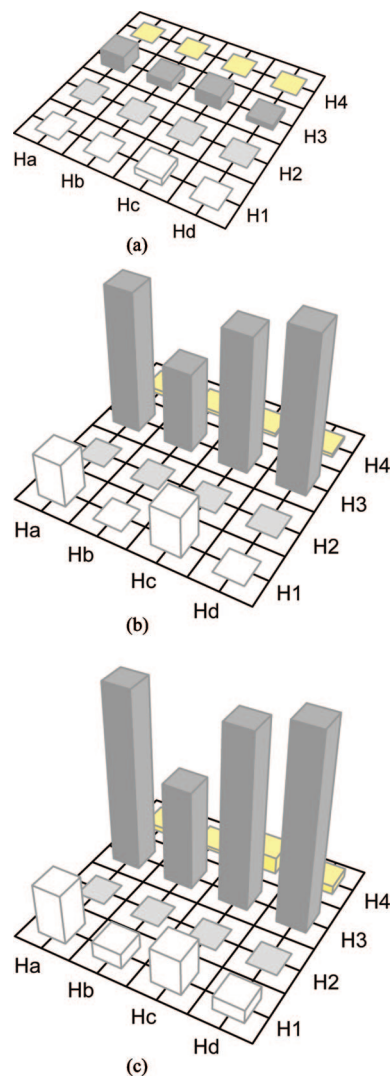
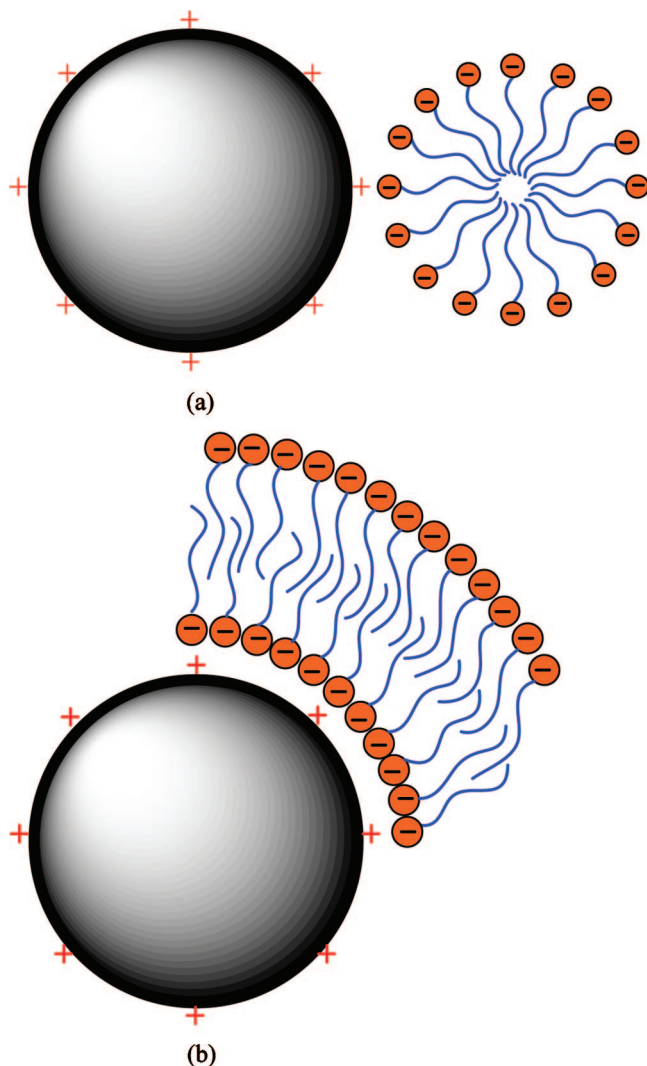


Figure 3. The relationship of cross-peak volume of **a**–**d**/**1**–**4** and mixing time (**a**, 100 ms; **b**, 300 ms; **c**, 500 ms). The SDS concentration is 2 mg/mL and the dendrimer/SDS mass ratio is 1. Strengths of the NOEs are given by the heights of the columns.

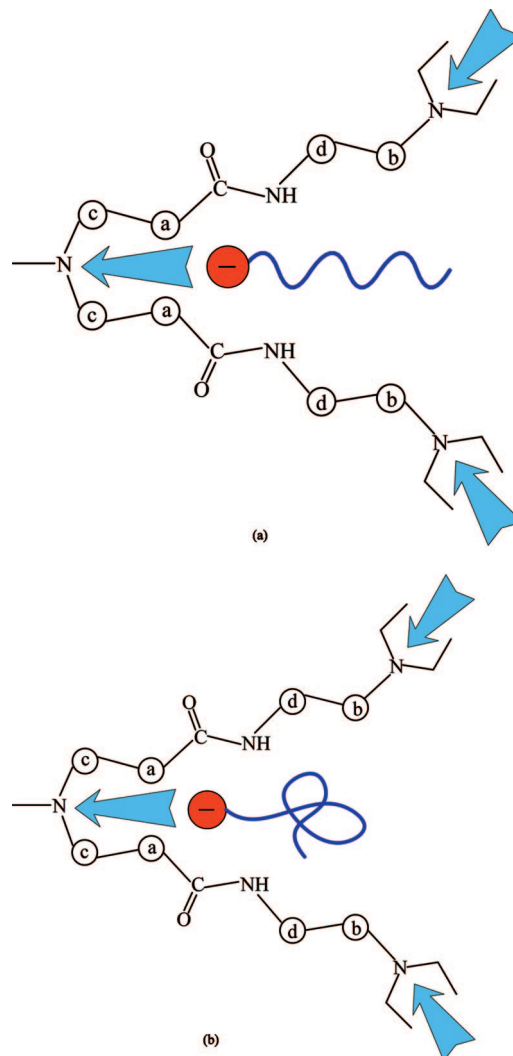
of SDS) by hydrogen-bond interactions. The hydrophilic surface functional groups can interact with oppositely charged guest molecules (hydrophilic head of surfactants) by electrostatic interactions. Previous studies have proposed the coexisting of two kinds of interactions between hydrophobically modified dendrimers and SDS: (1) electrostatic interactions between the negatively charged hydrophilic head of SDS and the protonized amine groups on the surface of dendrimers and (2) hydrophobic interactions between the hydrophobic tail of SDS and the hydrophobic regions on the dendrimer surface, which means the dendrimers are enlaced with SDS molecules.^{17–20} The electrostatic interaction is found to be the predominant contribution to form the dendrimer–SDS aggregations.^{17,24,26,27} However, the observed cross-peaks in this study cannot be interpreted by these interaction models, due to the following reasons: (1) the spatial distances between the protons (**3**–**4**) of SDS molecules located outside of dendrimers and the methylene protons of dendrimers are out of the limit of 5 Å, and (2) the cross-peak intensities of NOE interactions between protons (**1**, which localize nearest to dendrimer surface among the SDS protons, Scheme 1) of SDS and protons (**b'**, **d'**) of dendrimers should be much stronger than those between protons (**1**) of SDS and protons (**a**, **c**) of dendrimers, because protons (**b'**, **d'**) localize

SCHEME 1: Proposed models for the interactions between cationic dendrimers and anionic surfactants. Localization of SDS molecules on the surface of (a) lower generation dendrimers and (b) higher generation dendrimer



much nearer to the dendrimer surface than protons (a, c). This is difficult for us to believe when considering the reverse cross-peak intensities of them in our NOESY data (Figure 2). Furthermore, the PAMAM dendrimer-SDS solutions with different molar ratios in D₂O have a pH value of ~11 (Table S2 in the Supporting Information), so the NH₂ groups (pKs, 10) on the surface of dendrimers and the tertiary amine groups (pKs, 6–7) in the relative nonpolar pocket of dendrimers should be rarely charged or noncharged. Dendrimers may predominantly interact with the hydrophobic chain (protons 2–4) and the hydrophilic head (sulfate) of the SDS molecules by hydrophobic interactions or hydrogen-bond interactions at this pH. Therefore, the reasonable explanation for these results is the penetration of SDS molecules into the hydrophobic pockets of dendrimers. Since the pockets of dendrimers are congested and relatively nonpolar, the form of SDS inside dendrimers cannot be micellar, but monomeric. Unfortunately, as the peaks corresponding to the middle nine protons (3) of SDS are overlapped, the NOE intensities between these protons and dendrimers cannot be used to predict the detailed localization of SDS in the dendrimer pockets.

SCHEME 2: Proposed localization of SDS monomers inside the hydrophobic pockets of PAMAM dendrimers



Some hints can be found in the NOESY spectra of G5/SDS/D₂O, which points to the potential orientations of SDS molecules in the hydrophobic cavities; i.e., the presence of NOE signals of protons (1) of SDS and protons (a, c) of dendrimer, and the absence of cross-peaks between protons (2) of SDS and protons of dendrimer on the same contour map are observed in Figure 2. Since the NOE intensities of cross-peaks are proportional to the number N of equivalent protons and NOE/N is correlated with the interproton distance ($\text{NOE}/N \approx r^{-6}$), the results corroborate the spatially neighboring relationships of protons (1, $N = 2$) of SDS and protons of dendrimer in the complexes, and distant correlations of protons (2, $N = 2$) of SDS and protons of G5 dendrimer. Also, it can be found that the NOE intensities of cross-peaks between protons (1) of SDS and protons (a, c) of dendrimer are much stronger than that between protons (1) of SDS and protons (b, d) of dendrimer (Figure 2), suggesting that the hydrophilic head (sulfate group) of SDS may locate near the core or the boundary of each generation of dendrimers (Scheme 2a).

Besides, clear cross-peaks for NOE interactions between protons (1) and protons (3, 4) of SDS in the presence of G5 dendrimer (Figure 2 and Figure S1 of the Supporting Information) are observed, while no cross-peak for such interactions can be found in the spectra of free SDS/D₂O solution (Figure S2 of the Supporting Information) even at a higher SDS

concentration (8.3 mM for free SDS solution and 6.9 mM for dendrimer/SDS complexes), suggesting that the conformation of SDS molecules in aqueous medium is different from that in dendrimer–SDS aggregates.¹¹ The cross-peaks in the presence of dendrimers should be attributed to intermolecular or intramolecular NOE interactions of SDS monomers. It is rational that the intermolecular proximity causes the presence of these cross-peaks because the spatial distance between SDS monomers may be reduced in the dendrimer–SDS aggregates. If the intramolecular interaction of SDS also contributes to this cross-peak, then the hydrophobic chain of SDS must be in an energetically unfavorable conformation so that the methylene groups (**3**, **4**) can curve back to be close to protons (**1**) and the sulfate group. A possibility for this conformation is that the bended SDS chain localize in the smaller pockets to produce close contact between SDS and dendrimer protons (Scheme 2b). This explanation agrees well with the presence of cross-peaks between protons (**4**) of SDS and methylene protons of dendrimers in Figure 2. Therefore, the long hydrophobic tail of SDS may locate in the largest pockets of dendrimers or in smaller ones by bending their flexible chains into folding structures.

To investigate the effect of SDS concentration on its encapsulation process into PAMAM dendrimers, we obtained the NOESY spectra of G5/SDS mixtures with different ratios (Figure S3 of the Supporting Information, 2 mg/ml G5 being constant, the mass ratio of dendrimer and SDS ranges from 0.5 to 2). The intensities of cross-peaks between protons (**1**, **3**, **4**) of SDS and protons (**a**, **b**, **c**, **d**) of G5 dendrimer increase proportionally with the SDS concentration (Figure 2 and Figure S3 of the Supporting Information). Figure 4 shows the cross-sections along ω_1 taken at the position of protons (**1**) in the 2D-NOESY spectra for the G5/SDS solutions at different mass ratios. The increased signal intensity for the cross-peaks with increasing SDS concentration (Figure 5) clearly supports that more numbers of SDS monomers penetrate into the hydrophobic pockets of dendrimers at higher SDS concentrations.

For PAMAM dendrimers of different generations, their encapsulation behaviors toward SDS monomers may be different from each other. We compared the host behavior of G3/G6 dendrimer with G5 dendrimer under the same experimental conditions (Figure S4 in the Supporting Information, 2 mg G3 or G6 dendrimer in 1 mL D₂O, mass ratio of SDS/dendrimer is 1, mixing time is 300 ms). Intense cross-peaks between protons (**3**) of SDS and protons (**a**, **b**, **c** and **d**) of G3/G6 dendrimer are observed, suggesting the existence of SDS monomers in the interior of G3/G6 dendrimer. Considering the congested, relatively nonpolar cavities and closed structure of the G6 dendrimer, previous studies have suggested the absence of host–guest interactions between charged surfactants and the interior of G6 dendrimer at pH values well above the pKs of the interior tertiary amines.¹² However, our NOESY results in Figure S4b of the Supporting Information definitely demonstrate the presence of surfactants inside the hydrophobic pockets of the G6 dendrimer. Surprisingly, the encapsulation behavior of G3 dendrimer in Figure S4a of the Supporting Information is also different from previous results for PAMAM dendrimer/small guest systems where the G3 dendrimer is not capable of encapsulating guests.³⁰ Furthermore, the cross-peaks at chemical shift assigned to protons (**4**) of SDS molecules with protons of dendrimer are present in the NOESY spectrum of G5/SDS solution (Figure 2) but disappear in that of G3/SDS (Figure S4a of the Supporting Information) and G6/SDS (Figure S4b of the Supporting Information) solutions at the same mixing time. As shown in Table S1 of the Supporting Information, the numbers

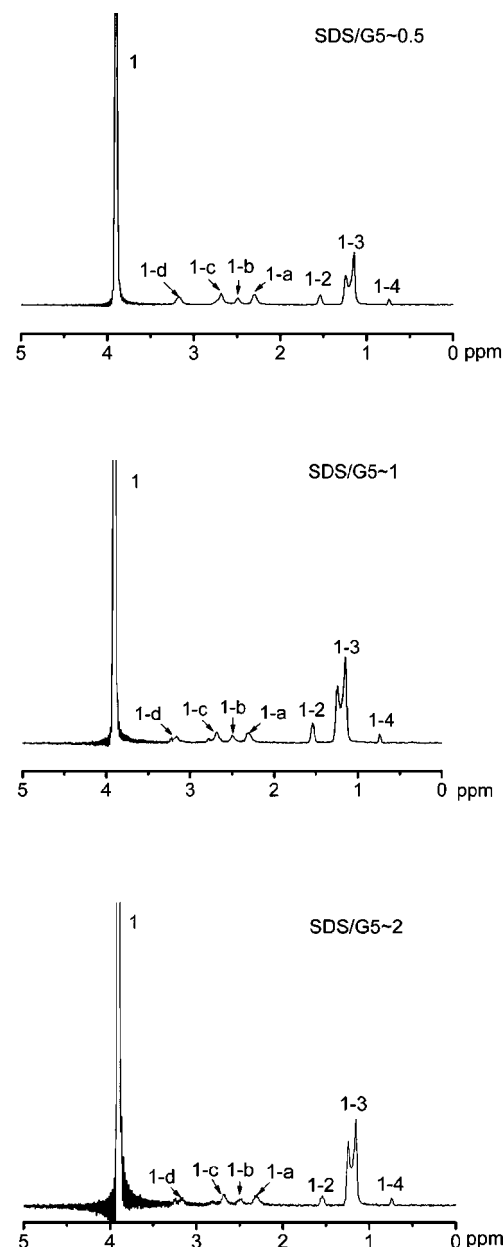


Figure 4. Cross-sections taken at the position of protons (**1**) along the ω_1 from the 2D-NOESY spectra of G5/SDS/D₂O solution in Figure 2 and Figure S3 of the Supporting Information.

of primary amine, tertiary amine, and the repeated unit of dendrimers, and the amount of SDS monomers added to the dendrimer solution are nearly the same for these NOESY samples. The differences on the cross-peaks for protons (**1**, **4**) of SDS and protons of dendrimer in the case of G5 and G3/G6 dendrimer are not caused by different components of dendrimer/SDS solutions, but due to distinct structures of different generations of dendrimers (G6 dendrimer possesses closed and congested structure, whereas the G3 dendrimer has open and relatively noncongested structure. For small guests, higher generation dendrimers are more capable of encapsulating the guests inside its pockets than lower generation dendrimers. However, this is different for larger guests such as SDS because of serious spatial hindrance during the formation of dendrimer–SDS inclusions. Therefore, G5 dendrimer may encapsulate more SDS molecules in its hydrophobic pockets than G3 and G6 dendrimers). This is further confirmed by the relatively weaker cross-peak intensities of NOE interactions between protons (**3**)

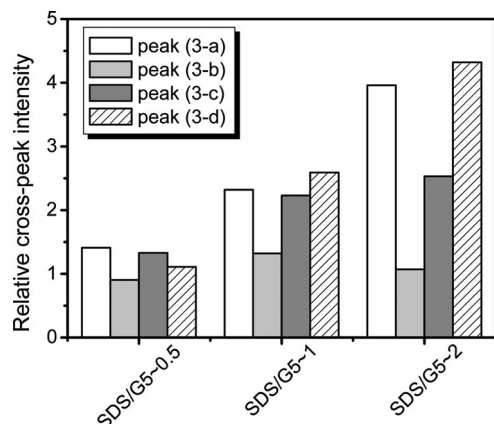


Figure 5. The relationship of cross-peak volume of $a \sim d/3$ and SDS concentration. The mixing time is 300 ms and the dendrimer/SDS mass ratio ranged from 0.5 to 2. Strengths of the NOEs are given by the heights of the columns.

of SDS and protons (**a**, **b**, **c**, **d**) of G3/G6 dendrimer in comparison with that in the case of G5 dendrimer.

To investigate the importance of dendrimer surface functionality on the encapsulation of SDS monomers inside dendrimer pockets, we compared the host behavior of amine-terminated G5 PAMAM dendrimer and carboxylate-terminated G4.5 PAMAM dendrimer (2 mg/ml dendrimer, the mass ratio of dendrimer and SDS is 1). G4.5 and G5 dendrimer were chosen because both dendrimers possess 128 surface functionalities, and similar molecular weights, sizes, and interior properties. As shown in Figure S5 of the Supporting Information, the cross-peaks between protons of SDS and protons of G4.5 dendrimer are not observed, suggesting that the encapsulation process is dependent on the surface charges of dendrimers. This is presumably due to the electrostatic repulsion forces between G4.5 dendrimers and SDS, which reduces the penetration process of SDS monomers into the interior of dendrimers. To further validate this conclusion, we compared the host behaviors of G5 dendrimer toward two kinds of surfactants with the same length of hydrophobic chain (12 carbon atoms): SDS, an anionic surfactant, and DTAB, a cationic surfactant. The absence of cross-peaks between protons of DTAB and protons of G5 dendrimer in the spectrum of G5/DTAB (Figure S6 of the Supporting Information) strongly suggested that the electrostatic repulsion forces between partially cationic charged dendrimer surface and positively charged DTAB prevent the encapsulation process, and that the encapsulation process is dependent on the charges of surfactants and dendrimers.

The interactions of dendrimers with surfactants have been extensively studied by several separate groups in the past decade. On the basis of these results, we can conclude that the aggregation process of the dendrimer-surfactant system has the following characteristics: (1) the assembly of surfactant molecules on the surface of dendrimers is mainly caused by electrostatic interactions between both species, (2) the assembly process occurs at a surfactant concentration (CAC) below the critical micellization concentration (CMC) of it, and the CAC of a surfactant in dendrimer solutions depends on dendrimer concentration, size, and surface charge, and (3) the final structure of the aggregates depends on dendrimer and surfactant concentration, dendrimer size, surface functional group, environmental temperature, and pH condition. In the presence of PAMAM dendrimers at a low concentration (less than 0.15 M), micelles form on the surface of lower generation ($<G4$) dendrimers, while bilayers of surfactants appear on the surface of higher

generation ($>G4$) dendrimers. However, the aggregate structures are definitely different if the concentration of dendrimers is above 0.15 M, where the bilayers of surfactants bridge more than one higher generation dendrimers, or alternatively, the micelles adsorb several lower generation dendrimers on the surface by electrostatic interactions^{13,21} (Scheme 1). However, the internal structures of the aggregates (inside dendrimers) were ignored in these studies. The only reference which referred to the potential of surfactant penetration into the relative nonpolar pockets of dendrimers used distinct dendrimers from traditional PAMAM dendrimers.¹⁶ These specific dendrimers allow the access of guests into their interiors even at large generations through the wedge created by the long hydrophobic chain (12 carbon atoms) at the core. From the fluorescence probe studies, C12-cored dendrimers were proposed to interact with the hydrophobic tail (inside) and hydrophilic head of SDS (outside) by hydrophobic and electrostatic interactions, while amine-cored dendrimers (C0) and EDA-cored dendrimers (C2) can only bind with SDS molecules on the surface by electrostatic interactions. This is hard to believe for us because this is not in accordance with our NOESY results. In terms of the fluorescence probe method, it cannot tell whether the SDS monomers actually penetrate into the pockets and closely bind with the interior scaffolds of the dendrimers. This problem can be easily resolved by the NOESY experiment. From the NOESY analysis, we conclude that the hydrophobic chain of surfactants localize in the hydrophobic pockets of dendrimers, and that the hydrophilic head as well as the terminal methyl group of the surfactant localize in close contact with the protons (**a**, **c**) of each generation of dendrimer. These results provide a new insight into the interactions between dendrimers and surfactants in comparison with previous investigations.

Conclusions

We investigated the interactions of surfactant (SDS and DTAB) with different generations of PAMAM dendrimers. The application of NOESY analysis points out a strong tendency for the long hydrophobic tails of these surfactants to associate with the hydrophobic pocket of dendrimers. The internal dendrimer-SDS interactions show the following features: (1) the sulfate and the methyl group of SDS localize near the core or the boundary of each generation of dendrimers; (2) the long hydrophobic chain of SDS monomers may locate in the larger pocket of dendrimers or in smaller ones by bending their flexible chains into folding structures; and (3) the encapsulation of surfactant by dendrimers is dependent on the dendrimer generation, dendrimer surface functionality, and surfactant concentration, as well as the surfactant charge.

Acknowledgment. We thank the Natural Science Foundation of Anhui Province (No. 070413112) and the Innovation Foundation from Hefei National Laboratory for Physical Sciences at Microscale (C07-06) for financial support of this program. Special thanks are given to Dr. C. Huang for kindly proof-reading the manuscript.

Supporting Information Available: This information is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) Tomalia, D. A. *Prog. Polym. Sci.* **2005**, *30*, 294.
- (2) Svenson, S.; Tomalia, D. A. *Adv. Drug Delivery Rev.* **2005**, *57*, 2106.
- (3) Esfand, R.; Tomalia, D. A. *Drug Discovery Today* **2001**, *6*, 427.

- (4) Caminade, A.; Laurent, R.; Majoral, J. *Adv. Drug Delivery Rev.* **2005**, *57*, 2130.
- (5) Cheng, Y. Y.; Xu, Z. H.; Ma, M. L.; Xu, T. W. *J. Pharm. Sci.* **2008**, *97*, 123.
- (6) Cheng, Y. Y.; Wang, J. R.; Rao, T. L.; He, X. X.; Xu, T. W. *Front. Biosci.* **2008**, *13*, 1447.
- (7) Cheng, Y. Y.; Gao, Y.; Rao, T. L.; Li, Y. W.; Xu, T. W. *Comb. Chem. High Throughput Screening* **2007**, *10*, 336.
- (8) D'Emanuele, A.; Attwood, D. *Adv. Drug Delivery Rev.* **2005**, *57*, 2147.
- (9) Gillies, E. R.; Frechet, J. M. J. *Drug Discovery Today* **2005**, *10*, 35.
- (10) Gupta, U.; Agashe, H. B.; Asthana, A.; Jain, N. K. *Biomacromolecules* **2006**, *7*, 649.
- (11) Caminati, G.; Turro, N. J.; Tomalia, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 8515.
- (12) Sidhu, J.; Bloor, D. M.; Couderc-Azouani, S. C.; Penfold, J.; Holzwarth, J. F.; Wyn-Jones, E. *Langmuir* **2004**, *20*, 9320.
- (13) Ottaviani, M. F.; Andechaga, P.; Turro, N. J.; Tomalia, D. A. *J. Phys. Chem. B* **1997**, *101*, 6057.
- (14) Bakshi, M. S.; Kaura, A.; Sood, R.; Kaur, G.; Yoshimura, T.; Torigoe, K.; Esumi, K. *Colloids and Surf., A* **2005**, *266*, 181.
- (15) Bakshi, M. S.; Kaura, A. *J. Colloid Interface Sci.* **2005**, *284*, 680.
- (16) Watkins, D. M.; Sayed-Sweet, Y.; Klimash, J. W.; Turro, N. J.; Tomalia, D. A. *Langmuir* **1997**, *13*, 3136.
- (17) Esumi, K.; Saika, R.; Miyazaki, M.; Torigoe, K.; Koide, Y. *Colloids and Surf., A* **2000**, *166*, 115.
- (18) Esumi, K.; Kuwabara, K.; Chiba, T.; Kobayashi, F.; Mizutani, H.; Torigoe, K. *Colloids and Surf., A* **2002**, *197*, 141.
- (19) Mizutani, H.; Torigoe, K.; Esumi, K. *J. Colloid Interface Sci.* **2002**, *248*, 493.
- (20) Yamokazu, Y.; Fukai, J.; Mizutani, H.; Esumi, K. *J. Colloid Interface Sci.* **2002**, *255*, 428.
- (21) Ottaviani, M. F.; Turro, N. J.; Jockusch, S.; Tomalia, D. A. *Colloids and Surf., A* **1996**, *115*, 9.
- (22) Bakshi, M. S.; Sood, R.; Ranganathan, R.; Shin, P. *Colloid Polym. Sci.* **2005**, *284*, 58.
- (23) Bakshi, M. S.; Kaura, A.; Miller, J. D.; Paruchiuri, V. K. *J. Colloid Interface Sci.* **2004**, *278*, 472.
- (24) Bakshi, M. S.; Sood, R. *Colloids and Surf., A* **2004**, *233*, 203.
- (25) Bakshi, M. S.; Sood, R. *Colloids and Surf., A* **2004**, *237*, 125.
- (26) Bakshi, M. S.; Kaur, G.; Mahajan, R. K.; Yoshimura, T.; Esumi, K. *Colloids and Surf., A* **2004**, *246*, 39.
- (27) Bakshi, M. S.; Kaura, A. *Colloids and Surf., A* **2004**, *244*, 45.
- (28) Bakshi, M. S.; Sood, R. *Colloids and Surf., A* **2004**, *244*, 159.
- (29) Tzeng, J. K.; Hou, S. S. *Macromolecules* **2008**, *41*, 1281.
- (30) Cheng, Y. Y.; Wu, Q. L.; Li, Y. W.; Xu, T. W. *J. Phys. Chem. B.* **2008**, *112*, 8884.

JP804954J