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The effect of chain packing on surfactant aggregation in aqueous solution

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Abstract - Hydrophobic interactions provide the main driving force for the aggregation of amphiphilic compounds in water. However, the morphology and dynamic properties of the aggregate represent the outcome of a compromise between a variety of partly opposing factors. It is obvious that efficient alkyl chain packing in the interior of the molecular assembly is a prerequisite for stabilisation. Unfortunately, the highly dynamic nature of micelles and smaller aggregates hampers a straightforward experimental approach. Small amphiphilic molecules like t-BuOH, 2-butoxyethanol (2-BE), and N-cyclohexylpyrrolidone (CHP) start to form highly dynamic, small clusters at the critical hydrophobic interaction concentration (chic). In addition to other techniques, the occurrence of a chic can be probed using kinetic studies of suitable model reactions. A detailed study of the aggregation behavior of a series of 1-alkyl-4-(C_{12}-alkyl)pyridinium iodides (1-11) illustrates that the preferred morphology of the aqueous surfactant assemblies is primarily determined by the molecular architecture of the surfactant molecule. Depending on the branching and stiffness of the 4-(C_{12}-alkyl) moiety, the length of the 1-alkyl substituent and the surfactant concentration, the surfactants form spherical micelles, rod-like micelles or vesicles. These differences in aggregation behavior are rationalized by considering the variation of the packing parameter of the surfactant monomer as a function of surfactant structure. The chain packing in the core of the spherical micelles was probed by an analysis of proton T_1 relaxation times within the framework of Wennerström's two-step model.

INTRODUCTION

Water is the ubiquitous solvent for life processes and the most precious chemical on our planet. Its unique, but not anomalous (ref.1), solvent properties originate from the strong intermolecular hydrogen bonding interactions in the liquid which allow the formation of large 3-dimensional hydrogen bond networks (ref.2). This explains the high cohesive energy density of liquid water. Yet water is quite different from other solvents which are strongly intermolecularly associated. The difference is, that the 3-dimensional "water structure" undergoes highly temperature-sensitive fluctuations between structures of different geometry and density. Thus, detailed knowledge of the temperature dependence of the effective potential barrier hindering rotational motions of water molecules (ref.1) is of paramount importance for an understanding of the properties of the liquid. For aqueous solutions, the fluctuations are most clearly reflected in characteristic heat capacities of hydrophobic solutes in water (ref.3). The strong hydrogen-bonding ability of water, as contrasted with its inability to participate in significant London dispersion interactions, is the main reason why the introduction of alkyl chains into water is thermodynamically unfavorable. Transfer of an alkyl moiety from the ideal gas to an infinitely dilute aqueous solution is accompanied by a positive Gibbs energy, a positive enthalpy, a large, negative entropy and a very large, positive heat capacity. These findings have been rationalized in terms of enhanced structuring of water molecules in the hydration shell around the apolar solute. This process is called "hydrophobic hydration" and is

supported by experimental evidence (ref.4) and by molecular dynamics (ref.5,6) and Monte Carlo statistical mechanics computer simulations (ref.7). Bringing alkyl groups together leads to hydrophobic interaction (ref.4). The favorable Gibbs energy of this association primarily stems from repulsions between the alkyl group and water rather than from London dispersion interactions between both alkyl groups. Often, the association is a cooperative process leading to clusters of molecules in which the apolar parts of the components are more or less shielded from direct contact with water.

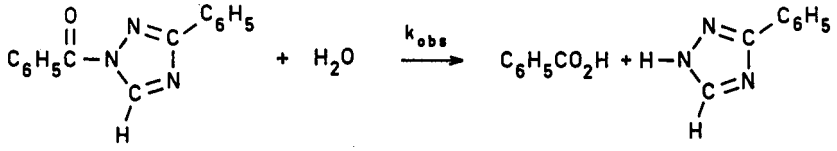
The cooperative aggregation has been extensively studied for surfactants, which are amphiphilic molecules with one or more alkyl chains ($>C_8$) attached to an ionic, zwitterionic or dipolar headgroup. A whole set of different morphologies is possible for the aggregate (ref.8). Spherical and rod-like micelles as well as bilayer vesicles are perhaps the most interesting representatives. Apart from their fundamental interest, micelle-forming surfactants find extensive industrial applications. Bilayer vesicles are of particular interest because of their successful use as simple and readily modifiable mimics for biological cell membranes ("membrane mimetic chemistry", ref.8).

It is obvious that the static and dynamic properties of these self-assembled systems will be highly dependent on the propensity for efficient packing of the alkyl chains in the interior of the aggregate. The conformation as well as the flexibility of the alkyl chain will be important parameters. In order to form a stable aggregate, hydrophobic interactions and other noncovalent interactions between the alkyl chains should dominate over the repulsions between the headgroups. Clearly the Gibbs energy of the aggregate represents a delicate compromise between opposing molecular forces determined by both the surfactant and the aqueous medium. Studies of the conformation and packing of alkyl groups have been performed using a variety of techniques, including NMR spectroscopy, X-ray and neutron diffraction, electron microscopy (EM) and both molecular dynamics and Monte Carlo statistical mechanics computer simulations. In this lecture, emphasis will be placed on some aspects of alkyl chain packing in aggregates of amphiphilic solutes which possess relatively short alkyl chains. No attempt will be made to review the vast literature on alkyl chain packing in surfactant aggregates. Only those aspects will be discussed which are of direct relevance for our recent physical organic research efforts in this area.

AGGREGATION OF SMALL AMPHIPHILIC MOLECULES

It has been recognized for a long time that highly aqueous mixtures of water and a relatively hydrophobic cosolvent exhibit peculiar solvent properties. Water-rich alcohol-water mixtures and particularly t-BuOH-H_2O are classical examples of such "typically aqueous" (TA) solutions (ref.4). Much emphasis has been placed on the concentration dependence of the apparent molar heat capacity which is quite similar to that of surfactant molecules (ref. 9). This behavior has been interpreted in terms of large structural changes in the water-rich region of the binary solutions. For 2-butoxyethanol(2-BE)-H_2O the heat capacity data were indicative for pseudo-phase separation, which means that the mixture thermodynamically behaves as if two microphases coexist in the solution, one rich in water and the other one rich in 2-BE (ref.10). Water-rich (WR) and cosolvent-rich (CR) microphases were also postulated for several other aqueous binary systems (ref.11). Evidence for microheterogeneities was also obtained from light-scattering studies (ref.12), NMR spin-lattice relaxation times (ref.13), ultrasonic absorption measurements (ref.14) and molecular dynamics computer simulations (ref.15). Formation of highly dynamic clusters with small mean association numbers, at least partly stabilized by solvent-separated interactions, is akin to micellization and has been analyzed in terms of a clathrate model (ref.11,16). These clusters are sometimes called "moving units", which are defined as groups of molecules which move together for a time much longer than the velocity auto-correlation time (ref.17). NMR spectroscopic studies indicate rapid exchange of 2-BE between the WR and CR microphases. Desrosiers et al (ref. 18) propose, based on NMR chemical shifts, that the conformer population in the CR microphase is different from that in the pure liquid. Relative to aqueous solutions of 2-BE (WR phase), there is an increment in the population of trans conformers. This has also been found for aqueous surfactant assemblies and presumably reflects the tendency to maintain dense packing between the alkyl moieties. However, the 2-BE clusters are very short-lived and no more detailed information about the average alkyl chain packing in the CR microphase has been obtained. In this context, it is relevant to note that Menger (ref. 19) showed that the trans/gauche energy

difference for hydrocarbon chains does hardly respond to solvation effects. If clustering occurs, the situation will be different and the system will aim at a minimal Gibbs energy by adjusting several partly counteracting factors including shielding from water, intermolecular repulsion and attraction and intrinsic conformational preferences. Interestingly, kinetic studies (ref. 20) have also provided strong evidence for cooperative association of hydrophobic cosolvents at high water concentrations. For example, the pH-independent, water-catalyzed hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in t-BuOH-H_2O is retarded by increasing concentrations of the alcohol.



However, large changes in $\Delta^{\neq}H^{\ominus}$ and $\Delta^{\neq}S^{\ominus}$ set in only at a mole fraction of water (n_{H_2O}) of 0.98 (Fig.1)(ref. 21).

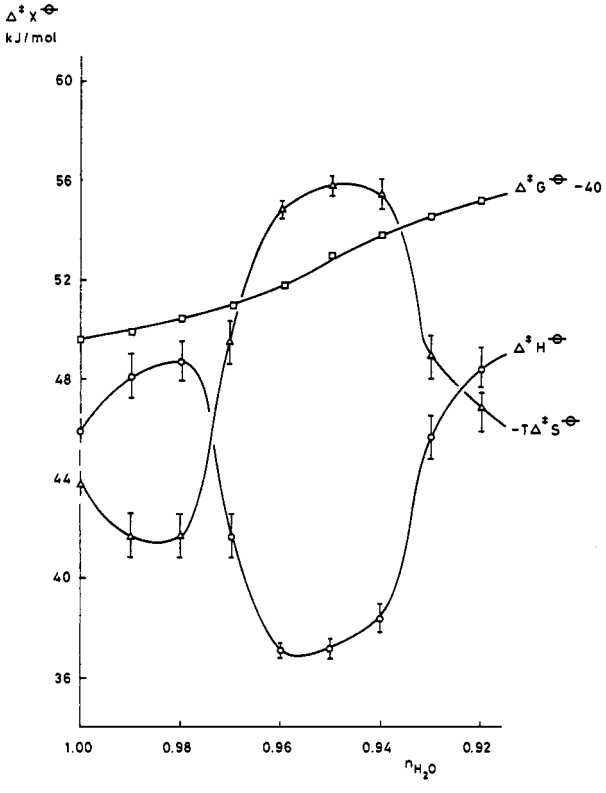
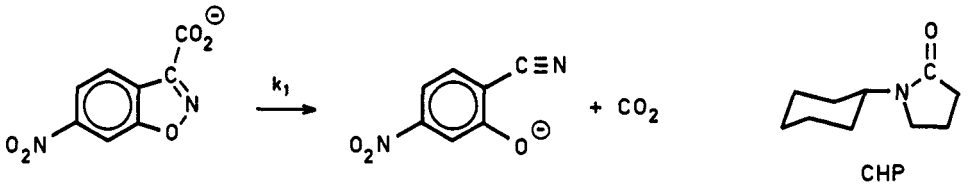


Fig. 1. Isobaric activation parameters for the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in water-rich t-BuOH-H_2O at 25°C

Most likely, this behavior signals binding of the substrate to clusters of t-BuOH which start to be formed in a cooperative manner at n_{H_2O} = 0.98. The corresponding concentration of the cosolvent has been termed the critical hydrophobic interaction concentration (chic) (ref.21). For t-BuOH, the chic is 1.4±0.3 M at 25°C. It is the concentration at which the hydrophobic hydration shells of the apolar part of the cosolvent begin to overlap appreciably, leading to cooperative association to small clusters. In terms of Grunwald's isodelphic/lyodelphic treatment of the solution thermodynamics of TA solutions (ref.22), the chic corresponds to the cosolvent concentration where $\delta\alpha/\delta m_2$ changes sign. Herein, α is a single microscopic variable characterizing the solvent network and m_2 is the cosolvent molality. If the cosolvent hydrophobicity is still further increased, the chic is expected to change to a lower value. This is borne out in practice. Using the unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate as a kinetic probe, it was found that the chic for N-cyclohexyl-2-pyrrolidone(CHP)-H_2O is 0.28±0.05 M at 30°C (ref.23). This exceptionally low



value, which almost approaches the critical micelle concentration (cmc) of ordinary surfactants, reflects the presence of 1 CH and 8 CH_2 moieties in CHP and the large hydrophobic hydration shell of the molecule. The plot of k_1 vs. n_{H_2O} is reminescent of similar plots of k vs. [surfactant] for micellar-catalyzed reactions (Fig.2). In addition to the kinetic data, the

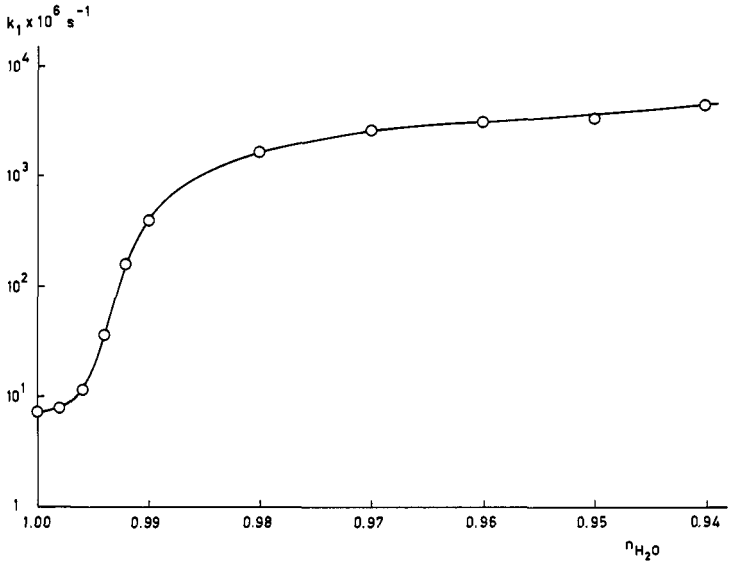


Fig. 2. Plot of k_1 vs. n_{H_2O} for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate in water-rich CHP-H_2O at 30°C.

occurrence of a chic for t-BuOH-H_2O and CHP-H_2O is also supported by spectroscopic measurements using Reichardt's $E_T(30)$ solvent polarity probe (ref. 23,24).
We note that a chic was also found for aqueous solutions of n-Bu_4NBr, using the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole as a kinetic probe (ref. 25). The concentration dependence of $\Delta^{\ddagger}H^{\ominus}$ and $-T\Delta^{\ddagger}S^{\ominus}$ (Fig.3) suggests a chic at 0.3 M of the salt (25°C), in reasonable accord with a calculation which takes into account the hydration numbers of the cation and anion. We now turn to aggregates of more defined structures: micelles and vesicles.

SURFACTANT AGGREGATION

Cooperative aggregation of surfactant molecules to form micelles starts at the critical micelle concentration (cmc) provided that the system is kept at or above the Krafft temperature (ref.26). The kinetics of micelle formation can be described in terms of two processes. The equilibrium between monomeric surfactant and micellar aggregate is characterized by a relaxation time τ_1 in the order of 10^{-3} - 10^{-8} s, depending on surfactant structure and concentration. Secondly, the formation or dissolution of a micelle is associated with a relaxation time τ_2 in the range 10^{-3} - 1 s. Apart from the nature of the surfactant, τ_2 values are dependent on temperature and salt concentration. Lively debates have centered around the question of micellar structure. Following the classical "oildrop model" (ref. 27), recent proposals include the "porous cluster" model (ref. 28), the surfactant block model (ref. 29), the lattice model (ref. 30) and the standard picture of ionic micelles (ref. 31). The last one is perhaps the most widely accepted

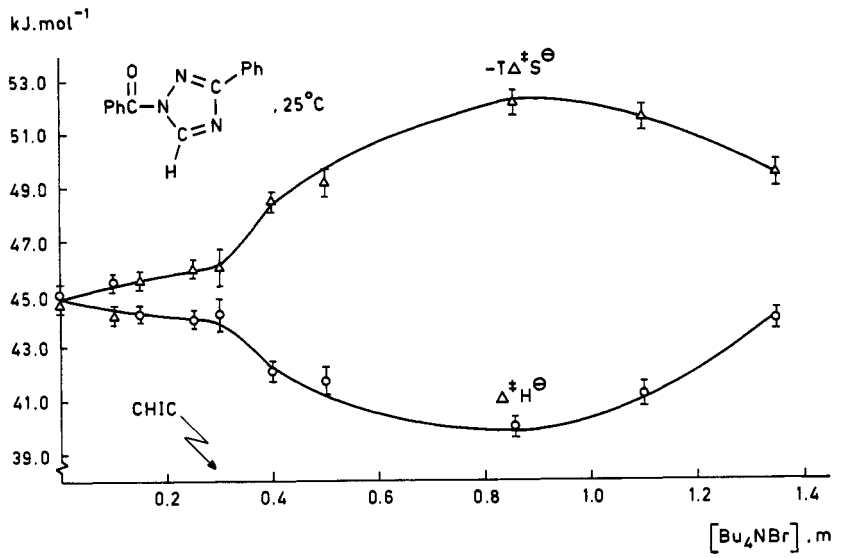
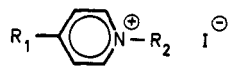


Fig. 3. Isobaric activation parameters for the neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole in aqueous solutions of n-Bu_4NBr at 25°C

model for a spherical micellar assembly. Depending on temperature, the surfactant structure, and the concentration of added electrolytes, the spherical micelle may grow into a cylindrical (rod-like) micelle at the critical rod concentration (crc). Recent kinetic studies of this transformation suggest that rod formation from CTAB occurs via successive association of monomers to the spherical micelle (ref. 32).
The interior of a micelle is liquid-like, e.g. the alkyl chain packing is disordered (ref. 26). This is largely based on comparison of molecular motion in micelles and in the liquid crystalline phase, the solubilization of nonpolar molecules in the micellar core, and NMR spectroscopic results (ref. 33). Particularly useful information has recently been obtained from ^{13}C, and ^{2}H and ^{1}H-NMR longitidual relaxation data. Analysis of these data in terms of the two-step model (ref. 34) yielded insight into the alkyl chain order and correlation times corresponding to the different dynamic processes in the micelle (lateral diffusion, micellar tumbling). Spectroscopic probe molecules have also been used frequently, but now ambiguities arise because of possible probe-induced disturbance of the micelle, uncertainties regarding the exact location and orientation of the probe and other problems. There is compelling ^{13}C-NMR evidence that the conformation of the alkyl chains differs from that in the neat hydrocarbon (ref. 35). The observed increase of the trans-to-gauche ratio (often most pronounced in the center of the alkyl chain) and back-folding of about 10% of the chain termini to the surface of the micelle are most likely governed by packing constraints in the surfactant assembly. Headgroup hydration and repulsion directly affect the packing of the alkyl chains near the micellar surface and usually at least one methylene moiety of the hydrocarbon chain is wetted. However, the extent of water penetration into the micellar core remains a topic of some controversy. It is clear that the exposure of a small part of the alkyl chains to water accounts for hydrophobic binding of sufficiently hydrophobic solutes to the micelle. Also nonionic, water-soluble polymers may bind to the micellar surface or penetrate deeper into the micellar interior (ref. 36,37).
In an attempt to probe the effect of alkyl chain branching and stiffness on micellar stability and morphology, we recently examined the aggregation behavior of a series of 1-alkyl-4-(C_{12}-alkyl)pyridinium iodides (1-11) in aqueous solution (Table 1) (ref. 38).



1 , $R_1 = (CH_2)_{11}CH_3$, $R_2 = CH_3$

2 , $R_1 = (CH_2)_4C{\equiv}C(CH_2)_5CH_3$, $R_2 = CH_3$

3 , $R_1 = CH(CH_3)(CH_2)_9CH_3$, $R_2 = CH_3$

4 , $R_1 = (CH_2)_8C(CH_3)_3$, $R_2 = CH_3$

5 , $R_1 = (CH_2)_7CH(CH_2CH_3)_2$, $R_2 = CH_3$

6 , $R_1 = CH_2CH(CH_2CH_2CH_2CH_2CH_3)_2$, $R_2 = CH_3$

7 , $R_1 = (CH_2)_{11}CH_3$, $R_2 = CH_2CH_3$

8 , $R_1 = (CH_2)_{11}CH_3$, $R_2 = (CH_2)_2CH_3$

9 , $R_1 = (CH_2)_{11}CH_3$, $R_2 = CH(CH_3)_2$

10 , $R_1 = (CH_2)_{11}CH_3$, $R_2 = (CH_2)_3CH_3$

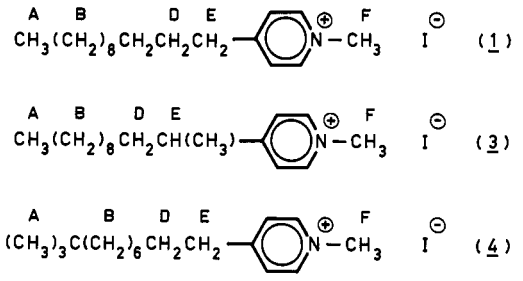
11 , $R_1 = (CH_2)_{11}CH_3$, $R_2 = (CH_2)_5CH_3$

TABLE 1. Surfactant and aggregate properties of 1 - 11.

	Aggregate morphology[a]	P*	cmc x 10^3 mol.kg^{-1}[b]	crc x 10^3 mol.kg^{-1}[c]	crc/cmc	β[d] %	λ_m^{CT} nm,CH_2Cl_2	λ_m^{CT} nm,SM
1	SM,RM	0.36	2.50	45	18.0	83	350	286
2	SM		13[g]			78	355	
3	SM	0.29	4.17	>440	>105	80	352	
4	SM,RM	0.53	3.93	25	6.4	84	352	293
5	SM,RM	0.58	3.76	30	8.0	80	354	286
6	V	0.91					355	[i]
7	SM,RM	[e]	2.21	37	16.7	79	351	286
8	SM,RM	[e]	1.91	28	14.7	79	354	290
9	SM,RM	[e]	1.93	30	15.5	76	350	286
10	SM,V	[f]	1.54	~4.5[h]		79	354	287
11	V	[f]		~0.8[h]			354	[i]

[a] SM = spherical micelle, RM = rod-like micelle, V = vesicle. [b] In H_2O at 30°C. [c] In D_2O at 30°C. For 4 the same crc was found in H_2O at 30°C. [d] Counterion binding for SM (from conductivity data, see ref. 38). [e] P* is 0.36 or slightly smaller, compare ref. 50. [f] P* is highly dependent on the headgroup conformation. [g] In H_2O at 25°. [h] Critical vesicle concentration in H_2O at 30°C. [i] No reproducible values were obtained because of light scattering problems.

The following surfactant and aggregate properties were examined: (i) the aggregate morphology as a function of surfactant concentration; (ii) the shape of the surfactant monomer as expressed in the critical packing parameter $P = V/a_o l_c$. Herein is V the volume of the hydrocarbon chain, a_o is the optimal surface area per monomer, and l_c is the critical chain length (ref.33). The exact values for these parameters are a matter of some concern. Assuming complete counterion binding and no headgroup hydration, we have calculated apparent packing parameters P* for 1 and 3 - 6 using CPK models. We contend that P* values will be proportional to P's and at least represent, in a semi-quantitative way, changes in the critical packing parameter; (iii) the cmc, crc (critical rod concentration), and β (counterion binding); (iv) the wave length (λ_m^{CT}) of the intramolecular charge-transfer (CT) absorption band, both for the monomeric surfactant in CH_2Cl_2 and for the spherical micelle. As discussed previously (ref. 39), λ_m^{CT} (micelle) is an intrinsic micropolarity probe for the microenvironment near the headgroups. Let us first compare the data for the 1-methyl-4-(C_{12}-alkyl)pyridinium iodides 1, and 3 - 6. Summation of the hydrophobic fragmental constants (ref.40) of the C_{12}-alkyl groups indicates that the hydrophobicities of the alkyl chains are very similar, irrespective of the branching. However, it is anticipated that branching will directly affect the packing and order in the micellar interior. Yet, the cmc's are quite similar and indicate only insignificant changes in micellar stability. Apparently, the surfactant molecules can adjust their packing regime in such a way that the overall stability of the assembly (cmc) as well as the properties of the headgroup region (λ_m^{CT},SM) do hardly respond to alkyl chain branching. T_1 NMR relaxation times of protons A-B and D-F in the surfactant molecules 1, 3, and 4 assembled in the spherical micelle have been analysed (ref. 41) in terms of Wennerström's two-step model (ref. 34). These data were then



employed to calculate order parameters S (Table 2) for the different sets of protons.

TABLE 2. Order parameters for the different surfactant protons in micellar 1, 3, and 4.

Proton	S(1)	S(3)	S(4)
A	0.07±0.01	0.08±0.01	0.10±0.01
B	0.12±0.02	0.13±0.02	0.18±0.02
D	0.14±0.02	0.25±0.03	0.18±0.02
E	0.11±0.01		0.18±0.02
F	0.07±0.01	0.06±0.01	0.07±0.02

The S values are a measure for the average orientation of the relevant H-H vectors for the different alkyl moieties (A-F) inside the micellar assembly (ref. 42). S is defined as

$$S = \tfrac{1}{2} < 3 \cos^2 \theta_{LD} - 1 >_t$$

in which θ_{LD} is the angle between the H-H vector and the local director, perpendicular to the micellar surface. The term $< 3 \cos^2\theta_{LD} - 1 >_t$ is a time average over the fast motions for one surfactant molecule in the aggregate. The order profiles (Table 2) for micellar 1, 3, and 4 are consistent with previous studies (ref.43) in which also the smallest S values were found at the end of the alkyl chain. In the three micelles, the same S applies for the protons F, which reinforces the notion that the orientation of the pyridinium ring with respect to the surface of the micelle is not affected by chain branching. The different conformation of the alkyl chain near the headgroup in 3 (vide supra) is reflected in an increase of S for protons D, but the average orientation of protons A and B is the same as that in 1. Interestingly, branching at the chain end (4) leads to an overall increase of the S values as compared with those in 1. An increased propensity of the bulky end group for backfolding to the micellar surface accounts for these results.

The effect of alkyl chain branching is most manifest in the ratio (crc)/(cmc) (Table 1). Branching near the headgroup (3) leads to a larger headgroup area and, most likely, the alkyl chain near the headgroup has now a preference for a gauche rather than a trans conformation as a result of the presence of the pyridinium ring bound to the relevant C-C bond (ref. 44). These effects lead to a large increase of the crc. By contrast, branching at the chain end (4,5) is associated with a decrease of the crc. Generally, rod-like micelles possess a smaller apolar surface area exposed to water than spherical micelles. This effect is counteracted by an increase in headgroup repulsion. Although entropy factors are not explicitly taken into account, our results show that the tendency to form rod-like micelles is associated with an increase of P* (Table 1), indicative for a more cylindrical shape of the surfactant monomer. Perhaps the best analysis of the sphere-to-rod transition has been couched in terms of the ladder model for surfactant aggregation (ref. 45). Surfactant 2 contains an acetylenic bond near the middle of the alkyl group. This will impose considerable stiffness in the hydrocarbon chain. The relatively large increase of the cmc mainly reflects the resulting effect on the effectiveness of the chain packing. However, the presence of the triple bond also slightly decreases the alkyl chain hydrophobicity and this factor may also contribute to the destabilization of the micelle. The aggregation behavior of 6 (P* = 0.91) is markedly different from that of 1 - 5. Above a critical concentration, 6 forms a turbid solution. Either heating to 38.5°C in water (or to 54°C in D_2O) or

sonication yields clear solutions. Both negative staining and freeze fracture electron microscopy revealed the formation of bilayer vesicles. These results indicate that **6** initially forms a lamellar phase which can be transformed into vesicles.
Vesicles of **6** were also obtained by the ethanol injection procedure (ref. 46). Thus, branching of the C_{12} - R_1 group in **6** leads to a large increase of P* and a pronounced tendency to form vesicles rather than micelles. In the past, vesicles have usually, but not always (ref. 47,48), been obtained from double-chain surfactants. In a sense, surfactant **6** may be viewed as a surfactant with two alkyl chains. But these chains are very short and the total number of carbon atoms in the apolar part of **6** is the same as that for the micelle-forming **1** - **5**. Thus our present results reinforce the notion that it is the shape of the surfactant molecule rather than the overall hydrophobicity or number of alkyl chains which determines the preferred morphology of the surfactant assembly. It should also be stressed that the change in preferred morphology of the aggregate for **6** is by no means a trivial one. As compared with the micelle, the bilayer vesicle has a much higher degree of order in the apolar core and the residence time of the surfactant molecule in the bilayer (ca.10^4s) is much higher (ref. 8). In fact, these vesicles formed from simple, synthetic surfactants exhibit the typical membrane properties of phospholipid vesicles (ref.8), including polymorphism, fast lateral and slow flip-flop movement of the amphiphile in the bilayer, osmotic activity, and fusogenic activity (ref. 49).
Variation of the N-alkyl substituent (**1**, **7** - **11**) also leads to drastic changes in aggregation behavior. Surfactants **1** and **7** - **10** form spherical micelles just above their cmc's. The log(cmc) values increase linearly with the hydrophobicity of the R_2 group as expressed in the sum of their hydrophobic fragmental constants (Σf_i; ref. 40). At higher concentrations, the spherical micelles formed from **1** and **7** - **9** are transformed into rods and now log(crc) is again linear with Σf_i. The small variation in (crc)/(cmc) in this series indicates that the headgroup surface area remains almost constant and that the 1-alkyl group extends into the aqueous Stern layer of the micelle. However, in the case of **10**, which carries an n-butyl group, the spherical micelles grow into a lamellar phase at the critical vesicle concentration (cvc). As in the case of **6**, the lamellar phase of **10** can be transformed easily into bilayer vesicles. The change in aggregation behavior for **10** is in accord with the notion that an n-Bu chain is the shortest alkyl chain that can fold back into the interior of the aggregate (ref. 50). For micelles formed from **1** and **7** - **9** the 1-alkyl group is almost fully exposed to water in the Stern layer. Backfolding of R_2 in the case of **10** obviously increases P* and induces preferential formation of vesicles at the cvc. As anticipated, the n-hexyl group in **11** also folds back and now the surfactant aggregates directly into a lamellar phase which can be readily converted into bilayer vesicles.

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