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Review

# Structural transition in micelles: novel insight into microenvironmental changes in polarity and dynamics

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ABSTRACT

Structural transitions involving shape changes play an important role in cellular physiology. Such transition can be conveniently induced in charged micelles by increasing ionic strength of the medium. Shape changes have recently been shown to result in altered packing and lowering of micellar polarity. As a consequence of reduced polarity, the ionization states of micelle-bound molecules vary in micelles of different shape. The changes in micellar organization and dynamics due to structural transition can be effectively monitored utilizing the red edge excitation shift (REES). These changes are influenced by the position (location) of the probe in the micelle, *i.e.*, the region of the micelle being monitored. Changes in organization and dynamics of probes and peptides upon structural transition are discussed with representative examples. We envisage that the reduction in micellar polarity and tighter packing upon structural transition represent important factors in the incorporation of drugs in micelles (nano-carriers), since micellar polarity plays a crucial role in the incorporation of drugs.



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## 1. Micelles: organized molecular assemblies suitable for optical spectroscopy

Detergents are important in the context of biological membranes due to their ability to solubilize membrane proteins and receptors (Chattopadhyay et al., 2002; Seddon et al., 2004; Kalipatnapu and Chattopadhyay, 2005). They are soluble amphiphiles and above a critical concentration (strictly speaking, a narrow concentration range), known as the critical micelle concentration (CMC), self-associate to form thermodynamically stable, noncovalent, nano-sized colloidal aggregates called micelles, at temperatures above the critical micelle temperature (CMT) (Helenius and Simons, 1975; Tanford, 1978). Micelles are widely used as membrane-mimetic systems to characterize membrane proteins and peptides (Sham et al., 2003; Raghuraman and Chattopadhyay, 2004; Rajagopalan and Rajarathnam, 2004; Rawat et al., 2005) and as vehicles for drug delivery (Narang et al., 2007; Katragadda et al., 2011). Studies on micellar organization and dynamics assume relevance since the general principle underlying the formation of micelles (*i.e.*, the hydrophobic effect) is common to other related assemblies such as reverse micelles, bilayers, liposomes, and biological membranes (Tanford, 1978; Israelachvili et al., 1980). Micelles are highly cooperative, organized molecular assemblies (nanostructures) of amphiphiles, yet dynamic in nature (Menger, 1979). The organization and dynamics of micellar environments, namely, the core, the interface, and the immediate layers of water on the interface, have been investigated using experimental and theoretical approaches (Sterpone et al., 2006).

*Abbreviations:* CMC, critical micelle concentration; CMT, critical micelle temperature; ESR, electron spin resonance; NBD, 7-nitrobenz-2-oxa-1,3-diazol-4-yl; NBD-cholesterol, 25-[N-[(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-methyl]amino]-27-norcholesterol; NBD-PE, N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine); REES, red edge excitation shift; SDS, sodium dodecyl sulfate; TOE, tryptophan octyl ester.

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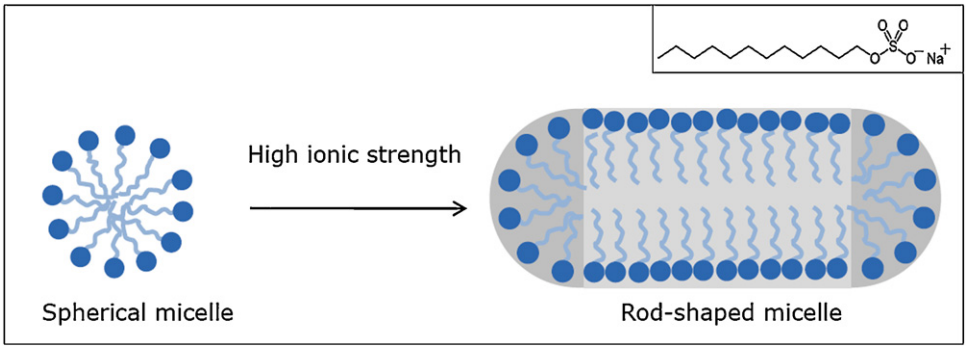


**Fig. 1.** Structural (sphere-to-rod) transition in charged micelles induced by high ionic strength. The structural transition takes place in charged micelles (such as SDS micelles; inset shows the chemical structure of SDS) at concentrations well above the critical micelle concentration. It should be noted that the microenvironment and packing for micelle-bound molecules in rod-shaped micelles are heterogeneous and are shown as spherical 'end caps' (darker shade) and the cylindrical central part (lighter shade). The headgroup spacing is reduced in the cylindrical part of the rod-shaped micelle due to attenuation of charge interactions at high ionic strength.
Adapted and modified from Chaudhuri et al. (2009).

It is well established that practically all types of molecules have a surface-seeking tendency in micelles due to very large surface area to volume ratio and that the interfacial region is the preferred site for solubilization, even for hydrophobic molecules (Shobha et al., 1989). In addition, they offer certain inherent advantages in fluorescence studies over membranes since micelles are smaller and optically transparent, have well-defined sizes, and are relatively scatter-free. Micelles can be of any desired charge type and can adopt different shapes and internal packing, depending on the chemical structures of the constituent monomers and the ionic strength of the medium (Mazer et al., 1976; Young et al., 1978; Hayashi and Ikeda, 1980; Raghuraman and Chattopadhyay, 2004).

## 2. Structural transition in charged micelles: change in micellar polarity

Structural transition (shape change) can be induced in charged micelles at a given temperature by increasing ionic strength of the medium or amphiphile concentration (Mazer et al., 1976; Young et al., 1978; Hayashi and Ikeda, 1980; Rawat and Chattopadhyay, 1999; Shobini et al., 2003; Heerklotz et al., 2004; Geng et al., 2005; Rawat et al., 2005; Chaudhuri et al., 2009; Paul and Guchhait, 2011). For example, spherical micelles of sodium dodecyl sulfate (SDS) that exist in water at concentrations higher than CMC assume an elongated rod-like (prolate) structure in presence of high electrolyte (salt) concentrations when interactions among the charged headgroups are attenuated due to the added salt (see Fig. 1). This is known as sphere-to-rod transition (Missel et al., 1984). This shape change induced by increased salt concentration is accompanied by a reduction in CMC (Chattopadhyay and London, 1984). Micellar sphere-to-rod transition can be explained in terms of the packing model described by Israelachvili (1991).

Interestingly, it has been suggested that large and elongated rod-shaped micelles are better models for biomembranes since the orientation of the hydrocarbon chains are more ordered in these micelles (Israelachvili, 1991; Rawat and Chattopadhyay, 1999; Heerklotz et al., 2004), perhaps due to the release of curvature stress encountered in spherical micelles. This was recently supported by monitoring the change in organization and dynamics associated with shape change (sphere-to-rod transition) of SDS micelles utilizing pyrene fluorescence (Chaudhuri et al., 2009). The fluorescence emission spectrum of the hydrophobic probe pyrene is sensitive to environmental polarity (see Fig. 2a; Dong and Winnik, 1982). It has been previously shown that pyrene is localized predominantly in the interfacial region in micelles (Menger, 1979; Shobha et al., 1989; Konuk et al., 1989). Interestingly, this is the region of the micelle that is sensitive to polarity changes due to water penetration. Utilizing changes in the ratio of polarity-sensitive pyrene vibronic peak intensities ($I_1/I_3$; see Fig. 2b), the apparent dielectric constant experienced by pyrene in spherical SDS micelles (in absence of salt) was found to be ~32, based on a calibration plot of pyrene vibronic peak intensity ratio in solvents of varying polarity. The apparent micellar dielectric constant displayed a reduction with increasing ionic strength and the dielectric constant in rod-shaped micelles of SDS (in presence of 0.5 M NaCl) was estimated to be ~22 (Chaudhuri et al., 2009). The reduction in polarity upon micellar shape change could be attributed to a decrease in micellar water content due to attenuation of the electrostatic repulsion between negatively charged headgroups of SDS (resulting in a reduction in headgroup spacing, see below). Importantly, the apparent dielectric constant for rod-shaped micelles compares well with the apparent polarity of hippocampal (Saxena et al., 2008) and model (Shrivastava et al., 2008) membranes.

In addition, pyrene forms excimers with very different fluorescence characteristics and the ratio of excimer/monomer is known to be dependent on monomer lateral distribution and host dynamics (Vanderkooi and Callis, 1974; Ioffe and Gorbenko, 2005), although the exact mechanism of excimerization is not clear (Blackwell et al., 1986). An analysis of the increase in pyrene excimer/monomer ratio accompanied with micellar shape change (see Fig. 2c) indicated an increase in average number of pyrene molecules per micelle associated with the sphere-to-rod structural transition (Chaudhuri et al., 2009). This is due to a combination of (i) a reduction in CMC (from 8.2 mM in case of spherical SDS micelles to 0.5 mM for rod-like micelles), (ii) an increase in aggregation number (from 62 in spherical SDS micelles to 480 in rod-shaped micelles), and (iii) the accompanying reduction in headgroup spacing which results in tighter packing of detergent monomers in the micellar assembly, enabling more monomers to pack in each micelle that ultimately results in shape change at higher ionic strength.

The reduction in polarity associated with micellar structural transition also influences the ionization state of micelle-bound molecules. This was apparent when the ionization behavior of an amphiphilic tryptophan analogue, tryptophan octyl ester (TOE, see Fig. 3), was monitored in micelles of different shape (Arora-Sharawat and Chattopadhyay, 2007). TOE represents an important model for membrane-bound tryptophan residues. The fluorescence characteristics of TOE incorporated into model membranes and membrane-mimetic systems have been shown to be similar to that of membrane-bound tryptophans (Ladokhin and Holloway, 1995; Chattopadhyay et al., 1997, 2005; de Foresta et al., 1999; Sengupta and Sengupta, 2000). TOE fluorescence is known to be sensitive to

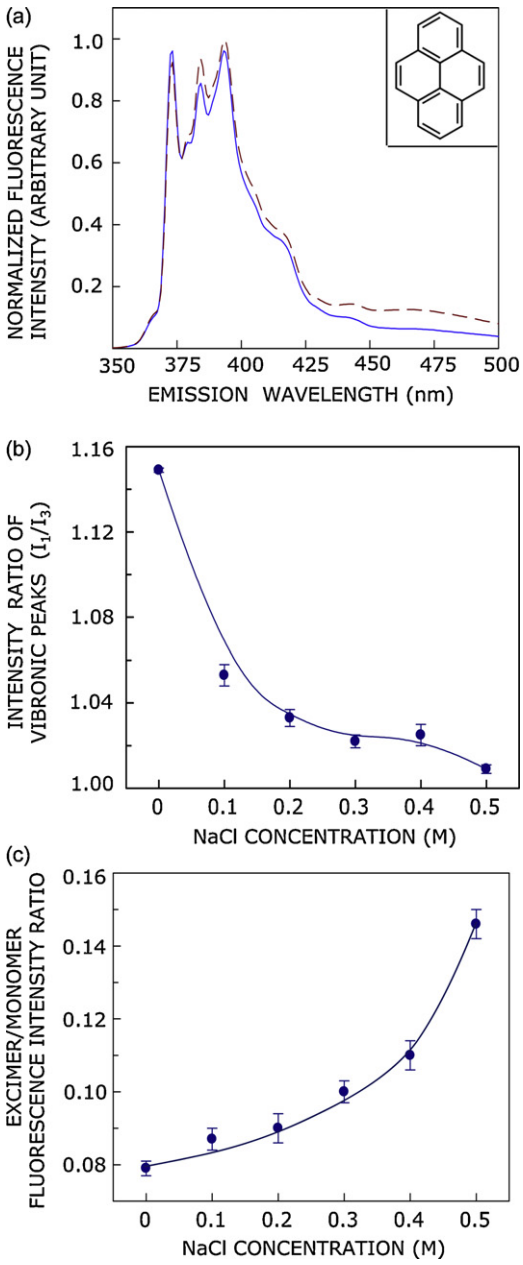


**Fig. 2.** Change in micellar polarity and packing induced by structural transition monitored using pyrene fluorescence. (a) Intensity-normalized fluorescence emission spectra of pyrene in SDS micelles in the absence (solid line), and presence (broken line) of high salt. The polarity-sensitive vibronic peaks are clearly seen in the spectra. Inset shows the chemical structure of pyrene. (b) The vibronic features of the emission spectrum of pyrene is known to be sensitive to environmental polarity. The figure shows the change in fluorescence intensity ratio of the first (373 nm) and third (384 nm) vibronic peaks of pyrene ($I_1/I_3$) in SDS micelles as a function of increasing ionic strength. (c) The excimer/monomer intensity ratio of pyrene fluorescence is indicative of monomer distribution in the host assembly. The figure shows pyrene excimer/monomer ratio in SDS micelles as a function of increasing ionic strength.

Adapted and modified from Chaudhuri et al. (2009). See text for other details.

pH (Chattopadhyay et al., 1997). This property of TOE fluorescence was utilized to monitor the ionization of TOE in micelles of varying shape (see Fig. 3). The apparent p$K_a$ for the α-amino group of the micelle-bound TOE was found to be ~9.5 in the spherical SDS micelles and ~8.7 in rod-shaped micelles. The difference in p$K_a$ of micelle-bound TOE clearly indicates different microenvironments experienced by the fluorophore in the two types of micelles.

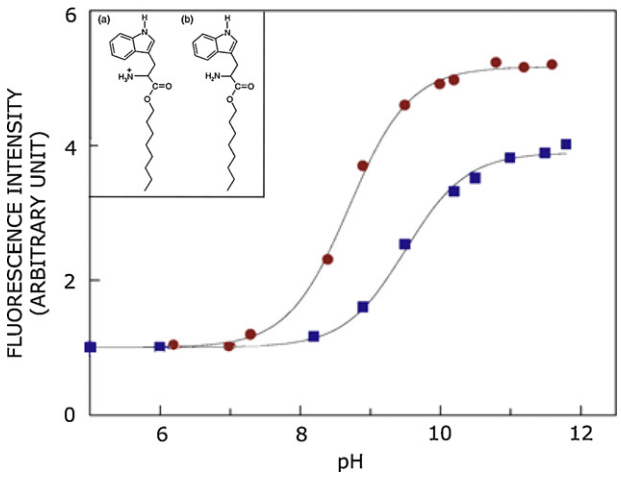


**Fig. 3.** Ionization state of micelle-bound TOE is sensitive to structural transition. The figure shows fluorescence intensity of TOE in SDS micelles in the absence (square) and presence (circle) of high salt as a function of pH. Inset shows the chemical structures of (a) protonated and (b) deprotonated forms of TOE.

Adapted and modified from Arora-Sharawat and Chattopadhyay (2007). See text for other details.

Micellar structural transition has also been explored utilizing electron spin resonance (ESR) spectroscopy (Ranganathan et al., 2001). Reduction in micellar polarity upon structural transition has been shown by ESR spectroscopy. The isotropic hyperfine coupling constant of nitroxide spin probes in SDS micelles exhibits reduction upon increase in micellar size as a function of ionic strength, implying that shape transition leads to a reduction in polarity (Bales et al., 1998). In addition, structural transition in charged micelles has been addressed by Fourier transform infrared spectroscopy (Weers and Scheuing, 1990). In this approach, micellar shape change can be monitored by the changes in the frequency and shape of $CH_2$ stretching bands. These measurements revealed that there is a decrease in the gauche conformer content of the methylene chains implying ordering in the cylindrical portion of the micelles (Scheuing and Weers, 1990). Recently, molecular dynamics simulations have provided complementary information regarding micellar shape transition (Sammalkorpi et al., 2009; Sangwai and Sureshkumar, 2011).

## 3. Structural transition monitored by the red edge excitation shift: change in organization and dynamics

Red edge excitation shift (REES) represents a powerful approach that can be used to directly monitor the environment and dynamics around a fluorophore in an organized molecular assembly (for reviews, see Mukherjee and Chattopadhyay, 1995; Demchenko, 2002, 2008; Chattopadhyay, 2003; Haldar and Chattopadhyay, 2011; Haldar et al., 2011). Organized molecular assemblies (such as micelles) can be considered as large cooperative units with characteristics very different from the individual structural units that constitute them. A direct consequence of such organization is the restriction imposed on the mobility of their constituent structural units. Interestingly, restriction (confinement) helps to couple the motion of solvent (water) molecules with the slow moving molecules in the host assembly (Bhattacharyya and Bagchi, 2000; Jha et al., 2011). In this scenario, REES represents a unique approach, which relies on slow solvent reorientation in the excited state of a fluorophore that can be used to monitor the environment and dynamics around a fluorophore in an organized molecular assembly. A shift in the wavelength of maximum fluorescence emission toward higher wavelengths, caused by a shift in the excitation wavelength toward the red edge of absorption band, is termed red

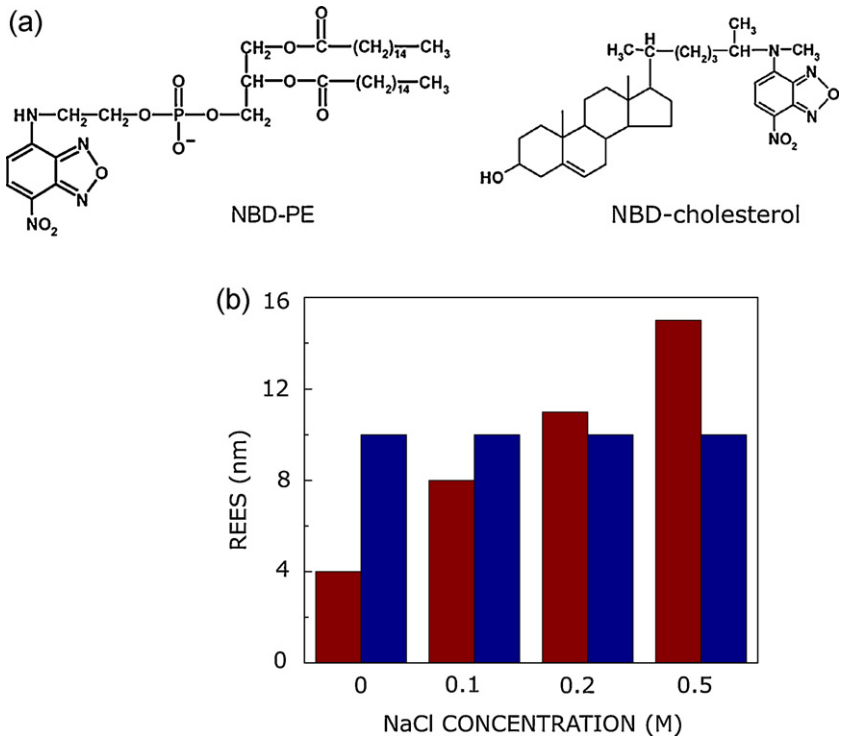


**Fig. 4.** (a) Chemical structures of NBD probes. (b) Depth-dependent solvent relaxation (REES) of differentially localized fluorophores in micelles of varying shape induced by increasing ionic strength. The magnitude of REES exhibited by NBD-PE (blue) and NBD-cholesterol (maroon) is shown. The NBD group of NBD-PE localizes at the micellar interfacial region while that of NBD-cholesterol resides at the deeper micellar core.
Data taken from Rawat and Chattopadhyay (1999). See text for other details.

edge excitation shift. This effect is mostly observed with polar fluorophores in motionally restricted environments where the dipolar relaxation time for the solvent shell around a fluorophore is comparable to or longer than its fluorescence lifetime. REES arises due to slow rates of solvent relaxation (reorientation) around an excited state fluorophore, which depends on the motional restriction imposed on the solvent molecules [or the dipolar environment, as in green fluorescent protein (Haldar and Chattopadhyay, 2007)] in the immediate vicinity of the fluorophore. This approach allows to assess the rotational mobility of the environment itself (which is represented by the relaxing solvent molecules) utilizing the fluorophore *merely* as a reporter group. In addition, since the ubiquitous solvent for biological systems is water, the information obtained in such cases will come from the otherwise 'optically silent' water molecules. A comprehensive treatment of the conceptual framework of REES is provided in our recent review (see Haldar et al., 2011).

As mentioned above, a direct consequence of organized molecular assemblies such as micelles is the restriction (confinement) imposed on the mobility of their constituent structural units. This feature of micellar organization makes it attractive for REES applications. The applicability of REES and related approaches [collectively termed as wavelength-selective fluorescence approach (Mukherjee and Chattopadhyay, 1995; Chattopadhyay, 2003; Raghuraman et al., 2005)] to a number of micellar systems varying in charge was explored using the interfacial fluorescence probe N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine) (NBD-PE; see Fig. 4a) (Rawat et al., 1997; Raghuraman et al., 2004). The choice of a suitable probe is crucial in REES studies of organized molecular assemblies (Haldar et al., 2011). The 7-nitrobenz-2-oxa-1,3-diazol-4-yl (NBD) group possesses some of the most desirable properties for serving as an excellent probe for both spectroscopic (Mukherjee and Chattopadhyay, 1996) as well as microscopic (Pucadyil et al., 2007) applications (for a review, see Chattopadhyay, 1990). It is very weakly fluorescent in water and upon transfer to hydrophobic media, it fluoresces brightly in the visible range and shows a large degree of environmental sensitivity (Chattopadhyay and London, 1988; Chattopadhyay, 1990; Lin and Struve, 1991; Fery-Forgues et al., 1993; Mukherjee et al., 1994). NBD-labeled lipids are widely used as fluorescent analogues of native lipids in biological and model membranes and in membrane-mimetic assemblies to study a variety of processes (Chattopadhyay, 1990; Mazères et al., 1996; Bertorelle et al., 2002). In NBD-PE (see Fig. 4a), the NBD group is covalently attached to the headgroup of a phosphatidylethanolamine molecule. The NBD group in NBD-PE has earlier been shown to be localized in the interfacial region of the membrane (Chattopadhyay and London, 1987, 1988; Mitra and Hammes, 1990; Wolf et al., 1992; Abrams and London, 1993) and its location in the micellar environment is believed to be interfacial. More importantly, we have earlier shown, using solvatochromic and quantum chemical approaches, that the dipole moment of the NBD group changes by ~4 D upon excitation (Mukherjee et al., 1994), an important criterion for a fluorophore to exhibit REES effects (Chattopadhyay, 2003; Haldar et al., 2011). Taken together, NBD-PE appears to be a suitable probe for REES measurements in micelles since the location of the NBD group in NBD-PE is expected to be interfacial, a region in the micellar organization that serves as the preferred site for solubilization and is characterized by unique dynamics of water molecules (Rawat et al., 1997). This was validated by the observation that NBD-PE exhibits REES in micelles of varying charge (Rawat et al., 1997). Interestingly, the magnitude of REES displayed by NBD-PE was found to be independent of micellar shape, *i.e.*, REES exhibited by NBD-PE in charged SDS micelles was invariant upon increase in ionic strength (see Fig. 4b). Since the change in micelle organization during such structural transition may not be limited to a particular region of the micelle, REES measurements were carried out after introducing fluorescent probes in

two distinct regions (the interfacial and the deeper hydrocarbon regions) of the micelle. In order to probe the effect of structural transition in the deeper hydrocarbon region of the micelle, REES measurements were performed with NBD-cholesterol in which the NBD group is covalently attached to the flexible acyl chain of the cholesterol molecule (see Fig. 4a). The NBD group of this molecule has been found to be localized in the hydrocarbon region of membranes (Chattopadhyay and London, 1987, 1988; Mukherjee and Chattopadhyay, 1996; Rukmini et al., 2001) and is expected to localize in the deeper hydrocarbon region in micelles. Due to its deeper location, the NBD group of NBD-cholesterol is capable of reporting solvation dynamics in the deeper regions of the organized molecular assembly in which it is incorporated. This is important since unlike bulk solvents, compartmentalized molecular assemblies are anisotropic in nature and therefore display differential solvent relaxation rates in different regions of the assembly (Chattopadhyay and Mukherjee, 1999a,b; Haldar et al., 2011; Haldar and Chattopadhyay, 2011). In contrast to what was observed in case of NBD-PE, the extent of REES of NBD-cholesterol in SDS micelles was found to be dependent on ionic strength, *i.e.*, shape transition (Rawat and Chattopadhyay, 1999). Interestingly, REES of NBD-cholesterol incorporated in SDS micelles displayed a progressive increase in the magnitude of REES with increasing ionic strength (see Fig. 4b) (Rawat and Chattopadhyay, 1999). This implies that the rate of solvent relaxation (reorientation) varies with probe location in the micelle. The above results show that the organizational change brought about by the sphere-to-rod transition has depth-dependent influence on micellar dynamics.

Confinement of a peptide within a restricted membrane-mimetic environment has been reported to increase the relative stability of the folded state against unfolded states due to reduction in dimensionality (Abel et al., 2006). This observation has potential biological relevance since intrinsically disordered proteins could be structured in their native cellular environment. In such a scenario, it becomes important to monitor the effects of hydration on the conformation and dynamics of proteins and peptides. Small peptides (such as gramicidin) are particularly suitable for such hydration studies due to high surface/volume ratio.

The linear peptide gramicidin forms prototypical ion channels specific for monovalent cations and has been extensively used to study the organization, dynamics, and function of membrane-spanning channels (Kelkar and Chattopadhyay, 2007). Gramicidin is a multitryptophan protein (Trp-9, 11, 13, and 15), which serves as an excellent model for transmembrane channels due to its small size, ready availability, and the relative ease with which chemical modifications can be performed. This makes gramicidin unique among small membrane-active peptides and provides the basis for its use to explore the principles that govern the folding and function of membrane-spanning channels in particular, and membrane proteins in general (Chattopadhyay and Kelkar, 2005). The unique sequence of alternating L- and D-chirality (see Fig. 5) renders gramicidin sensitive to the environment in which it is placed. The head-to-head (amino terminal-to-amino terminal) single-stranded $\beta^{6.3}$ helical dimer form is the cation conducting channel conformation of gramicidin in membranes. In this conformation, the carboxy terminus is exposed to the membrane–water interface and the amino terminus is buried in the hydrophobic core of the membrane. This places the tryptophan residues clustered at the membrane–water interface at the entrance to the channel (Ketchem et al., 1993; Mukherjee and Chattopadhyay, 1994).

The circular dichroism (CD) spectral characteristics of gramicidin incorporated in both spherical and rod-shaped SDS micelles are typical of the single-stranded $\beta^{6.3}$ conformation with two characteristic peaks of positive ellipticity at ~218 and 235 nm, and a valley at ~230 nm (Rawat et al., 2005; see Fig. 5a). The peaks are red shifted in the spherical micelles, probably due to increased

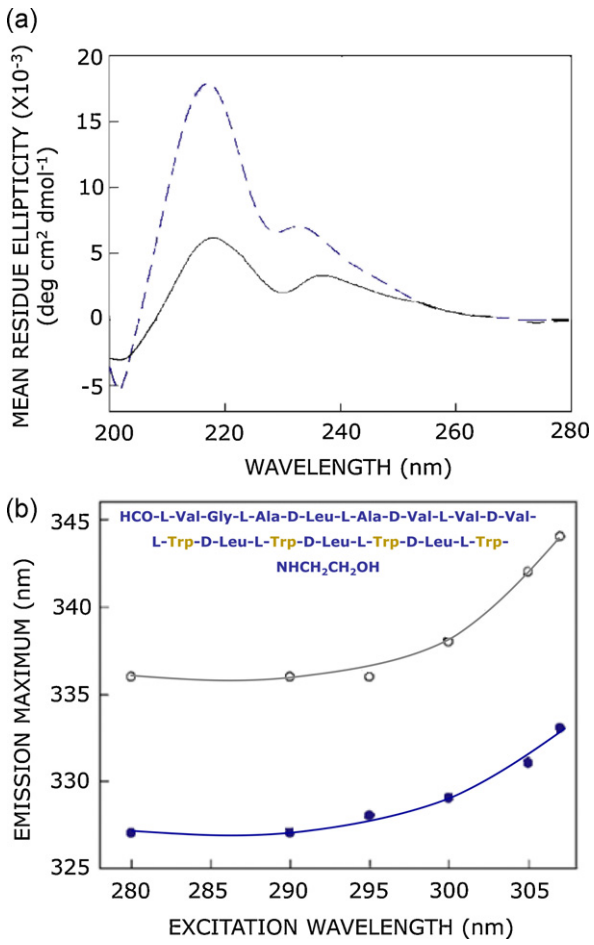


**Fig. 5.** Organization and dynamics of the ion-channel peptide gramicidin is sensitive to structural transition. (a) The figure shows the far-UV CD spectra of gramicidin in SDS micelles in the absence (solid line) and presence (dashed line) of high salt. (b) REES displayed by gramicidin tryptophans is sensitive to shape change. The figure shows the effect of excitation wavelength on the wavelength of maximum emission of gramicidin in spherical (empty circle) and rod-shaped (filled circle) SDS micelles. The amino acid sequence of gramicidin is also shown. Notice the unique alternating L- and D-chirality in gramicidin.

Data taken from Rawat et al. (2005). See text for other details.

water penetration as far-UV CD spectra of gramicidin are known to be sensitive to solvent polarity. The ellipticity at 218 nm is enhanced in rod-shaped micelles as compared to spherical micelles indicative of tighter (bilayer-like) packing in rod-shaped micelles that would reduce conformational heterogeneity and enhance secondary structural elements.

Fig. 5b shows that gramicidin tryptophans exhibit an emission maximum of 336 nm in spherical SDS micelles (in the absence of salt). Interestingly, the emission maximum of gramicidin in rod-shaped SDS micelles displays a blue shift and is at 327 nm. This indicates a reduction in polarity of the tryptophan environment in presence of salt, *i.e.*, in rod-shaped micelles (similar to what was observed with micelle-bound TOE, see above). This is possibly due to a decrease in water content as a result of tighter packing in rod-shaped micelles owing to neutralization of the charge on detergent headgroups by the counter ions. REES of gramicidin tryptophans bound to SDS micelles of different shape is shown in Fig. 5b. The figure shows that gramicidin tryptophans display REES of 8 nm (from 336 to 344 nm) in spherical micelles when the excitation wavelength was changed from 280 to 307 nm. This implies that the interfacial region of spherical SDS micelles (where gramicidin tryptophans are localized) offers considerable restriction to

reorientation of solvent dipoles around the excited state fluorophore. In rod-shaped SDS micelles, gramicidin exhibits REES of 6 nm (from 327 to 333 nm), corresponding to change in excitation wavelength from 280 to 307 nm (see Fig. 5b). These results highlight the difference in microenvironment experienced by gramicidin tryptophans in spherical and rod-shaped micelles. Taken together, these results using the well-characterized ion channel gramicidin, demonstrate that deformation of the host assembly (shape transition) could modulate peptide organization and dynamics. Interestingly, it has been previously shown that the conformation of membrane proteins such as cytochrome $b_5$ can depend on the size and curvature of the membrane vesicle to which it is bound (Greenhut et al., 1986).

## 4. Conclusion and future perspectives

Structural transitions involving shape changes play an important role in cellular physiology (Paluch and Heisenberg, 2009). For example, the shape of erythrocytes (red blood cells) has been shown to change with the pH and ionic strength of the medium (Rasia and Bollini, 1998). The shape of the erythrocyte is believed to be maintained by the membrane skeleton in close interaction with the plasma membrane (Luna and Hitt, 1992). Investigations into the role of the membrane in such shape changes have revealed that modification of either the membrane composition or the structure of its individual constituents can lead to shape changes (Kuypers et al., 1984). Alteration of cholesterol level, selective removal of phospholipids from the outer membrane leaflet, pH and membrane potential alterations, metabolic depletion, and introduction of lysophospholipids, fatty acids, and charged amphipathic agents in membranes leads to shape changes of erythrocytes (Kuypers et al., 1984; Backman et al., 1998; Gedde and Huestis, 1997). Shape changes can be induced even in liposomes by mechanical stress, temperature or pH variation, osmotic shock, and by asymmetric transmembrane distribution of phospholipids (Farge and Devaux, 1992). Shape changes in cellular membranes that occur due to modifications of membrane composition (Kuypers et al., 1984; Backman et al., 1998; Gedde and Huestis, 1997) can directly affect the function of membrane proteins such as mechanosensitive channels that respond to changes in membrane curvature (Perozo et al., 2002). For example, the function of the gramicidin channel has been shown to be sensitive to curvature changes of the membrane bilayer (Lundbaek et al., 1997). Interestingly, SDS micellar shape change induced by chlorpromazine, an amphiphilic cationic phenothiazine drug, has been reported (Caetano et al., 2002).

Micellar nanoparticles with a hydrophobic core and a hydrophilic shell are being increasingly used for efficient drug delivery (Torchilin, 2007; Lee et al., 2010). Interestingly, micellar polarity (dielectric constant) plays an important role in the incorporation (solubilizing capacity) of drugs (Rebagay and Deluca, 2006). In this context, the reduction in micellar polarity and tighter packing upon structural transition represent crucial factors in the incorporation (solubilizing capacity) of drugs in micelles used as nano-carriers for drug delivery (Rebagay and Deluca, 2006). Future research will focus on fine-tuning of shape and size of micellar nanoparticles to optimize micellar polarity with the overall goal of efficient drug delivery.

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