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Concentration dependent morphological transition of nanostructured self-assembly towards hydrogelation seeding from micellar aggregates through stereochemically optimized H-bonding network of amino acid derived cationic amphiphiles

Saubhik Haldar*, Koninika Karmakar

Department of Chemistry, Jadavpur University, Kolkata 700032, India

HIGHLIGHTS

- Concentration dependent morphological transition from micellar aggregates to hydrogelation.
- Stereochemically optimized H-bonding network amino acid derived cationic amphiphiles.
- Advent of wormlike micellar phase in absence of any added external stimuli.

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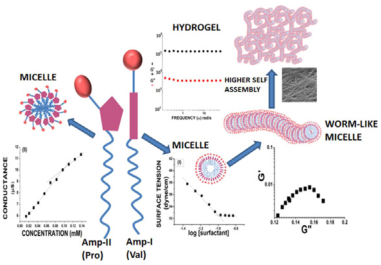
GRAPHICAL ABSTRACT



ABSTRACT

The present work describes the concentration dependent gradual transition of hierarchical-morphology of anisotropic self-assembly towards hydrogel network seeding from micellarization that is primarily effected by supramolecular H-bonded interaction of optimal structural orientation of amide segment embedded in an amino-acid based cationic amphiphile: $[Me_3N^+(CH_2)_3\text{-(L)Xaa-C(=O)}C_{15}H_{31}\ I^-$ where (L)Xaa = L-Val (**I**) and L-Pro (**II**)] in absence of any external stimuli. Surfactants (**I** and **II**) show micellar property evidenced from tensiometric, conductometric and fluorescence anisotropy studies. Unlike **II**, **I** shows considerable change in their aggregate phase from giant micellar to worm like micellar behavior characterized from "Cole-Cole" plot for Maxwell-fluids which on higher concentration (~3.5 mM) leads to hydrogel as observed in rheological studies [G' (storage modulus) > G" (loss modulus)] and presence of fibrous nano-structure in FESEM studies. The red shifted cotton band going from low to higher concentration for either of the amphiphiles suggests a conformational twist among the amide bonds rendering better packing arrangement. Both IR and CD studies signifies that the self-assembly of (**I**) is more like β-sheet type compared to (**II**) and can be rationalized based on their β-sheet stabilizing propensities whereas presence of Proline (a β-sheet breaker) with constrained cyclic pyrrolidine architecture, hinders the extended intermolecular H-bonding interaction.Such finer control over amphiphiles' architecture leading to an extensive hierarchical transition in self-assembly from micelles to worm like micelles and finally to hydrogel solely through optimized H-bonding network in absence of any external additives is unequivocally evidenced through tailor made synthesis and physicochemical characterization.

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* Corresponding author.
E-mail addresses: shaldar@chemistry.jdvu.ac.in, saubhikhaldar@gmail.com, s.haldar@rediffmail.com (S. Haldar).

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1. Introduction

Non-covalent interactions have been found to be the fundamental prerequisite for the bottom up approach of synthetic biology towards the molecular level understanding of structure–activity relationship; scientific quest has been continued over the years by various research groups. Addressing this diverse issue, *de novo* supramolecular systems have been designed to procure systems with predictable properties. Involvement of various non-covalent interactions like, intermolecular H-bonding, van der Waals, π-π and columbic interactions with inherent chirality, structurally diverse amino acid derived surfactants are found to exhibit distinctive physicochemical [1] and biologically active properties [2]. Self-assembly from tailor made molecular architecture shows its immense potential towards fabrication of well-organized nanostructured materials for a broad spectrum of applications, such as, self-assembly matrices for liposomal/niosomal targeting of drugs [3–5], generation of diverse nano-structures like micelles, vesicles, nanotubes, three dimensionally entangled gel networks [6–8] and also as an extra cellular matrix for tissue engineering [9,10]. Molecular self-assembly of surfactant system has been found to provide a powerful platform for the creation of well-organized nanostructures like micelles which under certain conditions such as concentration, salinity, temperature, presence of counterions, etc., can undergo uniaxial growth and form very long and highly flexible aggregates, referred to as “wormlike” or “threadlike” micelles [11]. In general, wormlike micelles (WLMs) have been mainly formed by mixing a surfactant (mostly cationic) and a low molecular weight hydrotrope (or primer) that screen the electrostatic repulsions between the surfactant charged headgroups, however, recent studies also highlight that both long-chain zwitterionic and non-ionic surfactants can form WLMs without the introduction of hydrotropes [12]. Earlier hydrogelation as well as organogelation in oils from pyridinium head group based cationic amphiphiles with embedded valine and isoleucine was accomplished by Hanabusa and his coworkers suggesting the importance of hydropobic factors and H-bonding interactions [13]. In our previous work, the vital role of non-covalent interactions was evidenced in the molecular organization of N-n-hexadecanoyl amino acid amphiphiles with hydrophobic Cα-side chains in Tris buffer (pH 9.3) [14]. Because of the significant potential of technological application of wormlike micelles and of hydrogel systems in biomedical applications especially in artificial extracellular materials (ECMs) for tissue engineering and the quest for rational understanding of structure function relationship of such hydrogels becomes a challenging area of modern research interests.

Despite, abundant information of hydrogel forming systems are prevalent in the literature, the morphological transition from milellar aggregate to hydrogel are majorly influenced by external additive like hydrotopes, however such transition of self-assembly network in absence of any external stimuli which primarily regulated supramolecularly interactive H-bonded network involving a single amino acid unit is significantly novel. The present study strongly emphasizes the viscoelastic wormlike micellar aggregate or even its elastic morphology can also be achieved from a single molecular unit and does not mandatorily require an externally added hydrotopes. A finer modulation of the amphiphile’s structure involving inter-molecularly interactive units has a significant role towards construction of the widely applicable WLMs and hydrogel systems. Since the design is made up of biocompatible molecular units, in the arena of biomimetic organic soft materials, such investigation not only suggest to looking into the *de novo* architecture of the molecular backbone but also can give the molecular level rational understanding of physicochemical and mechanical properties of tailor made systems.

2. Experimental

2.1. Materials

Palmitic acid, N-hydroxysuccinimide, triethylamine (NEt_3), Methyliodide, L-amino acids (valine and proline) were purchased from SRL, India and solvents (Pet. Ether, EtOH, MeOH, EtOAc, $CHCl_3$) were purchased from P.C. Industries, India. Solvents were freshly distilled before use. N,N-dimethylpropylenediamine, diphenylhexatriene (DPH) were purchased from Aldrich Chemical Co. USA. All the procured chemicals are analytical grade reagents and used without any further purification.

2.2. Synthesis

The schematic representation of the synthetic procedure has been given in Scheme 1.

2.3. Methods

2.3.1. Tensiometric studies

For tensiometric studies, de Noüy ring detachment method has been used. The platinum ring was cleaned with ethanol followed by acetone and the instrument was checked by measuring the surface tension of water before each experiment. Surfactant solutions were made in deionized water and the stock solution for each surfactant was maintained at 0.01(M). Typically 5 repeated measurements were made at each concentration and allowed to stand for 5 min after reaching the equilibrium at 30 °C. The reproducibility was examined periodically thermo stating to ± 0.1 °C using a JENCON INDIA circulating water bath.

2.3.2. Conductometric studies

The cmc was obtained as the break in the plot of the electrical conductivity against the surfactant concentration was measured using Thermo Scientific, Orion Star A215 (pH/conductivity) instrument. The cell constant 0.475 (cm^{-1}) was determined using a potassium chloride solution of known conductivity [15]. The conductivity cell was immersed in the surfactant solution. The concentration of the surfactant was progressively increased by successive additions of aliquots of a stock surfactant solution of concentration about 10 times larger than the cmc. The constancy of the temperature during a conductivity run was better than 0.1 °C. The cmc values were determined to within (3%). The plots of conductance against C were also used to determine the value of the micelle ionization degree at the cmc (α) [16].

2.3.3. Dynamic light scattering experiments

The DLS measurements were performed with a Malvern Nano-ZS instrument employing a 4 mW He–Ne laser ($\lambda = 632.8$ nm) and equipped with a thermostated sample chamber. A 1.0 mM solution of the amphiphile was prepared in de-ionised water. A Millipore Millex syringe filter (Triton free, 0.22 μm) was used for the filtration of the amphiphile solution and was used into the scattering cell (path length 1 cm). The operating procedure was programmed using DTS software in such a way that there were averages of 15 runs, each run being averaged for 10 s, and then a particular hydrodynamic diameter and size distribution was evaluated. All the light scattering measurements were performed at 25 ± 0.5 °C.

2.3.4. Steady-state fluorescence anisotropy measurements

The polarity of the microenvironment of the self-assemblies was evaluated using anisotropy of DPH embedded in the surfactant assembly in phosphate buffer. Being hydrophobic, DPH would like to reside more into the hydrophobic domain of the aggregates. The anisotropy (r) can be correlated to the microenvironment of