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Supramolecular association as the basis of materials design. Case studies with hydrogels and organogels*

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Abstract

Molecular designs of several low molecular mass gelators for aqueous and organic media are presented. We find that gelation requires strong intermolecular association, which eventually produces supramolecular networks. Solvent molecules get entrapped into these highly entangled networks, presumably due to surface tension. From a two-phase mixture comprising an upper oily layer of commercial fuels and a lower aqueous layer, *N*-Lauroyl-*L*-alanine is able to gelate the oil selectively.

Keywords: Amphiphiles, gels, self-assembly, protein lipidation.

1. Introduction

Amphiphilic molecules comprise a polar headgroup region that likes solvents like water and a tail-like region that does not. When suspended in water these molecules self-organize into thermodynamically stable aggregates that range from micelles, bilayers or a number of more complex self-assembled entities.[1] Another class of materials formed as a sequel of intra- or inter-molecular self-assembly is known as gels.[2, 3] Gels are found in both natural and man-made sources. For instance, 'Jell-O', a popular food, is a good example of gel. Protoplasm and animal flesh are other examples of gel. It is rather strange that despite gels being so commonplace, investigations relating the physical information on their molecular structure are rather limited. Several reasons could be attributed to this. For instance, gelators of water are usually large molecules (i.e. proteins and polymers) whose complicated intermolecular associations are often difficult to decipher. In addition, such interactions are generally not static but can change (often irreversibly) with time, thermal stimuli or mechanical stress. Moreover, materials in the gel-state cannot be studied by atomic resolution X-ray diffraction analysis, the main source of our most precise structural information.

It has been recently realized that certain low molecular mass, nonpolymeric molecules also possess the capacity to gelate specific solvents.[4–13] A few of this class of gel-forming molecules are also amphiphilic. Since gels derived from such low molecular mass systems are nonpolymeric and could often be synthesized by applying principles of self-assembly, they represent attractive systems for materials design. Consequently, de novo molecular design of such systems is attracting a lot of current attention.

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Due to our interest in the design of novel self-assembling molecular entities, we embarked upon a program of synthesizing supramolecular aggregates, which also possess the capacity to retain large volume of solvents. My presentation here is rather succinct as most of the work is already published. Interested reader can get details from the reference section pertaining to our publications in this area for experimental and other information.

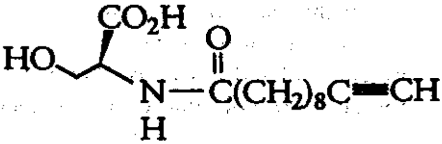
2. Background

We have been intrigued by protein lipidation in cellular surfaces, a phenomenon, which is responsible for sustaining the activity of several membrane-associated proteins.[14] Nonlipidated proteins are cytosolic, and hence biologically inactive. To address the origin of such questions at molecular level, we have been systematically examining the self-assembly properties of fatty acid amides of several natural amino acids.

Another phenomenon, which is commonly observed on cellular surfaces, involves carbohydrate-based modifications (glycosylation) at the *N*-terminus of proteins. These modified residues along with glycolipid assemblies have been implicated in diverse intercellular recognition events.[15] However, it is often difficult to isolate these lipids in pure form from natural sources. Therefore, it has been considered important to synthesize and examine chemically pure sugar-based amphiphiles that self-assemble in suitable solvents to produce membranous organizations. The self-organizing properties are strongly dependent on the molecular structures of such lipids. This is particularly relevant because naturally occurring monoglycosylated lipids cannot form stable bilayer membranes by themselves. A vesicle-forming supporting lipid is usually added to the glycolipid in order to produce stable bilayer vesicles.[16, 17] Several sugar-derived amphiphiles are also attracting attention recently due to their significant immunomodulatory and antineoplastic activities.[18, 19]

3. Our work

During the studies undertaken in my laboratory, it was found that a hydrophobically modified amino acid derivative, *N*-undecynoyl-*L*-serine, (**1**) formed fibrous microstructures and gel when dissolved in chloroform or other related chlorinated hydrocarbons.[20] Interestingly, the corresponding histidine amphiphile, (**2**) did not, however, produce any gelated materials in chlorinated hydrocarbons. It was also found that the corresponding olefinic and fully saturated fatty acyl derivatives of *L*-serine such as undecenoyl or undecanoyl compounds also induced similar gelation of the chlorinated hydrocarbons indicating the importance of the choice of amino acid at the headgroup in such amphiphiles in the induction of gelation. Subsequently, we synthesized the corresponding dimeric analogue by Glaser-type oxidative coupling of the



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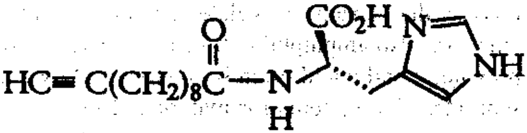

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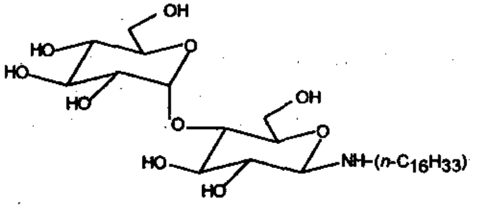
N-undecynoyl-*L*-serine derivative. This derivative did not produce gels in the above solvents although the same system when suspended in aqueous media produced tubular aggregates.

Subsequently, we synthesized a range of lipophilic derivatives of *L*-phenylalanine. Of these, only the *n*-hexadecylamide of *N*-benzyloxycarbonyl-*L*-phenyl alanine possessed the capacity to effectively gelate a number of organic solvents.[21, 22] By judicious variation of the protecting group around the *L*-phenyl alanine moiety of this derivative it was revealed that the presence of chirality, urethane and amide linkages was essential for effective gelation.[22]

Amphiphilic sugar derivatives have been interesting due to their significance in areas of self-assembly and molecular recognition in biological systems.[23] The sugar-linked amphiphiles are also often produced on a commercial scale and its starting materials are obtained from renewable raw materials.[24] The aldopyranose rings at the head group level of these molecules have multiple hydroxyl groups with defined orientation unlike their acyclic analogues. Consequently, the formation of strong cooperative hydrogen bonding networks between the amphiphiles is feasible. Spontaneous association of these amphiphiles is thus anticipated in water as a result of cooperating noncovalent forces, i.e. hydrogen bonds among sugar moieties and hydrophobic association between the long hydrocarbon chains. The pronounced chiral character of the headgroup should also help generate novel nonspheroidal microstructures.[25]

To develop novel water-gelating molecules, four single- and two double-chained disaccharide amphiphiles (**4-9**) were synthesized[26] and their hydrogel-forming behaviour was extensively investigated. These amphiphiles were based on maltose and lactose. Since the gels formed from some of these systems showed the ability to 'trap' water molecules upon gelation, they were described as 'hydrogels'. When these gels were heated to ~70°C, the samples turned into clear, isotropic fluids and upon gradual cooling, the hydrogels could be reproduced. Thus these systems were also 'thermo-reversible'. The low molecular mass (MW 565) of the gelators compared to that of a typical polymeric gelator-forming substance implies pronounced aggre-



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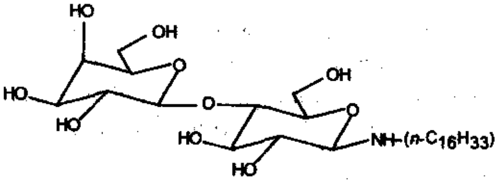

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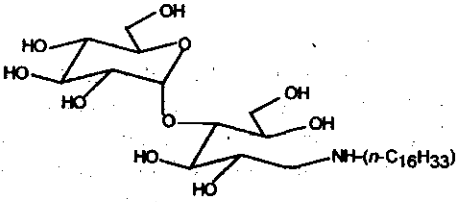

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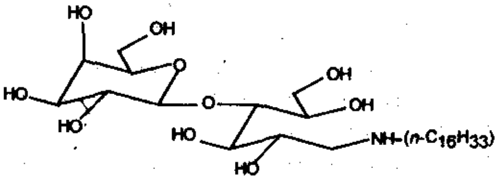

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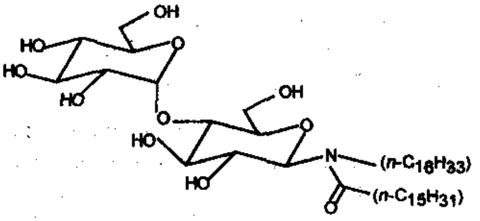
gation of the disaccharide amphiphiles into larger microstructures during gelation. In order to discern the aggregate textures and morphologies, the specimen hydrogel samples were examined by high-resolution scanning electron microscopy (SEM). SEM studies confirm the presence of fibrous structures in such hydrogels.

The possible reasons for the exceptionally high water-gelating capacities (> 6000 molecules of water per gelator molecule) exhibited by these *N*-alkyl disaccharide amphiphiles being the presence of large interlamellar spaces into which presumably the water molecules get entrapped due to surface tension. In contrast to their single-chain counterparts, the double-chain lactosyl and maltosylamine amphiphiles upon solubilization in EtOH-H_2O afforded hydrogels, with reduced mechanical strengths. Interestingly, the corresponding microstructures were found to be quite different from the corresponding hydrogels of their single-chain counterparts. Rheological studies provided further insights into the viscoelastic behavior of these hydrogels. Varying the chain length of the alcohol cosolvent could modulate the gelation capacities, melting temperatures and the mechanical properties of these hydrogels.



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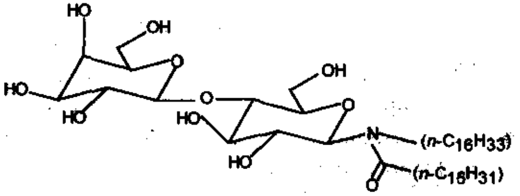

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Interestingly, variation in the conditions of the preparations of aqueous suspensions of the above compounds also afforded vesicular and related giant microstructures.[27] These aggregates maintained inner aqueous compartments as revealed from the dye entrapment studies. Some of these suspensions also manifested the ability to effectively complex transition metal ions.

Most recently, in our laboratory, a small biocompatible organic molecule has been shown for the first time to cause gelation of oil and organic solvents in preference to water.[28] The material, a simple amino acid derivative, *N*-lauroyl-*L*-alanine, could, with further modification, ultimately be used in the control of oil and other organic spills.

As discussed earlier, countless low molecular mass-gelating agents have been developed for transforming liquid organic solvents into a gelatinous state but these work preferentially only with a single compound, given a mixture of oil and water.[4–13] It has until now not been possible to gelate one component selectively over another. This is even more pertinent when one of those components is water.

The problem with gelating any organic solvent mixed with water is that often hydrogen bonding is required in order to form a gel network and water molecules simply compete for dominance when such noncovalent interactions are important. We discovered, however, that the fatty acid-derived amino acid, *N*-lauroyl-*L*-alanine, could simply and very effectively gelate nonpolar organic solvents such as aromatic and aliphatic hydrocarbons like hexane, benzene and petrol.

Scanning electron micrograph images of gels formed in both heptane and toluene revealed the existence of fibrous, entangled microstructures. We then figured that since the agent was so effective it might be worth experimenting with mixtures of solvents to see whether it would be possible to selectively gelate organic liquids through the formation of a three-dimensional fibrous network. It was also found that the gelator was dissolved by heating but as soon as the mixture returned to room temperature the oily layer was found to be completely gelated leaving the aqueous layer unaffected, a state maintained even after a week. This observation prompted us to model oil-spill conditions by violent agitation of the mixture. It was found that the heat–cool cycle still resulted in gelation of only the oil. At present, we are using a heating–cooling cycle to induce gelation with oil. But we do emphasize that these results point the way to a novel means of controlling oil and other toxic spillage once they can tweak the material to work passively or with an additive.

4. Conclusion

This is a brief account of our work on the design of gel-forming systems and on the systematic evaluation of their properties along with physical characterization of gels that are produced. It was established that for gelation, the molecule must possess the capacity to self-assemble in three-dimensions to form fibrous networks. Self-assembly of the cited molecules is evident from SEM studies. FT-IR studies have shown that this process involves specific interactions involving sites such as CO_2H and (O)=C-N-H, where each perpetuates aggregation along one axes. The 'third' axis most likely originates from Van der Waals contacts of the polymethylene chains in the ensemble.

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