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Functional self-assembled lipidic systems derived from renewable resources

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Abstract

Self-assembled lipidic amphiphile systems can create a variety of multi-functional soft materials with value-added properties. When employing natural reagents and following biocatalytic syntheses, self-assembling monomers may be inherently designed for degradation, making them potential alternatives to conventional and persistent polymers. By using non-covalent forces, self-assembled amphiphiles can form nanotubes, fibers, and other stimuli responsive architectures prime for further applied research and incorporation into commercial products. By viewing these lipid derivatives under a lens of green principles, there is the hope that in developing a structure–function relationship and functional smart materials that research may remain safe, economic, and efficient.

Keywords

Low molecular weight gels; Renewable reagents; Self-assembly; Smart materials; Stimuli responsive

1 Introduction

The assembly of lipids in biology indicates their varied functionality to both the supramolecular and lipid chemist [1]. While these two branches of chemistry do not always intersect, recent advances in materials science link efforts in the study of lipids and self-assembling structures [2]. Due to the wide range of lipids that occur in nature, often with small structural changes between them, these chemicals offer themselves as powerful tools in the study of the basic science of how molecules congregate. Furthermore, of interest to the technologist and engineer is the application of these assembled materials and the exploitation of their biological relevance. Compared to the wide array of supramolecular structures derived from petroleum-based resources, the ability to mine lipids from naturally

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renewable resources makes them of special interest as academia and industry buy into an emerging sustainable ideology: the Biorefinery Model.

Even before the advent of Green Chemistry and its principles, there was a wealth of research being done to create safe products in a green manner following the Biorefinery Model (Fig. 1) [3–5]. This model is similar to the structure and practices of the petroleum processing industry, though instead using biomass as its feedstock. In recent years, biorefineries have profited from using white biotechnology which employs whole cells and enzymes, utilizing nature's tools to work on nature's waste, something humans have been working at for a long time [6]. As nature's tools work very well with nature's products, the model advocates the use of resources from natural and renewable sources [7].

With the introduction of the 12 principles of Green Chemistry, researchers began to simultaneously focus on efficiency and safety when developing alternatives to hazardous products and wasteful procedures. One of the Biorefinery Model's heralded practices uses waste from anthropogenic processes to create value-added chemicals [8]. Waste remains a promising reagent precursor and chemists have begun to regain the title of alchemist by making it possible to transform your morning Starbucks into succinic acid [9].

Lipid chemists may even have trouble discerning these practices as green as they have been using self-organizing natural products for over a century [10, 11]. Lipid researchers continue to research systems as complex as our own phospholipid bilayers, what is better to work with than safe and efficient chemicals that possess specific characteristics for the application they desire [12, 13]?

The power of combining these two sub-disciplines' principles to lipid chemistry is that they enable a cascade of green consequences that in turn reduce the environmental, social or economic cost of each bond made and broken. Put more simply, by following both the rules of the Biorefinery Model and Green Chemistry, you have safer and more functional options. This in turn makes the study of chemistry, arguably a never-ending combinatorial experiment, more manageable for chemists and the world around them. By understanding self-assembly, a fascinatingly useful property of lipid systems, researchers can develop new functional smart materials from natural renewable resources.

2 Self-assembled functional systems

As it is difficult to guess the potential functionality of novel self-assembling structures, choosing amphiphilic building blocks is a tall order as the link between structure and function can be elusive. Just as an amphiphile's hydrophilicity and lipophilicity varies depending on the presence and position of functional groups, understanding renewable reagents may allow for the a priori design of smart materials [14, 15].

This review focuses on derivatives of the phenolic lipid mixture cardanol, sugars, sugar alcohols, acetaminophen, and ascorbic acid (Scheme 1) [2, 16, 17]. Chosen because of their mixture of saturated and unsaturated side chains, specific stereochemistry, or inherent functionality, each of the amphiphilic compounds self-assembles to form three-dimensional structures in solution. As self-assembled systems possess functionalities imparted not only

by the primary structure of the monomer, but also the secondary structures of the self-assembled systems, they have piqued the interest of theorists and experimentalists alike [18, 19]. Just as polymers may retain characteristic properties of their monomers so may the assembly of non-covalently bonded monomers, which are easily tuned with additional components to best create functional soft materials for a variety of applications [20–22].

A sugar's hydroxyl groups and a fatty acid's alkyl-chain can allow the resulting amphiphilic compound to self-assemble via non-covalent interactions [23]. These self-assembled systems may be fibers, ribbons, vesicles, or a wide variety of other structures based on the amphiphilic monomer and the solvent in which it assembles (Fig. 2). While monomers form polymers after being chemically activated, self-assembled structures of monomeric amphiphiles spontaneously assemble, aggregating in solution not to form amorphous precipitates, or three-dimensional crystals but fine nanoscale structures. While attractive non-covalent forces such as hydrogen bonding, van der Waals forces, and π - π stacking are much weaker than a polymer's covalent bonds, these weak forces allow for the creation of smart materials that are designed for degradation [3]. Furthermore, if an amphiphile is derived using a biological or biologically derived catalyst by following the Biorefinery Model, the amphiphiles are easily degraded through a back-reaction with the same catalyst in an alternative solvent, such as water, after its self-assembled system undergoes simple thermal or shear-induced disintegration into the monomeric amphiphiles [24, 25].

Employing aspects of Green Chemistry and the Biorefinery Model, it can be seen that these monomers, in comparison to traditional synthetic polymers, may be as easy to make but much easier to break making them viable chemical alternatives for next generation materials. By systematically exploring the assembly and assemblies of numerous biobased small molecules, the solution on how to forge a link between structure and function may assemble on its own.

2.1 Doubly polymerized cardanyl acrylate thin films

As self-assembled systems often consist of monomers with at least two components, it is important to understand the functionality and diversity of each. Before two-phase systems are discussed, it is useful to examine a simple one-component system: polymer films. Polymerized cardanyl acrylate (1) has been explored as a value-added chemical because of its ability to form two sets of covalent carbon-carbon bonds. The first form via the acrylate's vinyl moiety, and the second between cardanol's *cis*-unsaturations [26]. This was demonstrated by selectively activating the groups using different initiators. The vinyl moiety reacts with azobisisobutyronitrile in toluene or through atom transfer radical polymerization via ethyl-2-bromoisobutyrate [27, 28]. On the other side of the molecule, cardanol's unsaturated side chains self-crosslink after auto-oxidation in the presence of air, or exposure to UV light [29]. The first polymerization creates the linear acrylate-backbone polymer, while the second forms a methanol insoluble transparent film. Cardanol-derived polymers such as the phosphorylated Anorin-38 are used in surface coatings as alternatives to phenol/formaldehyde resins [30]. In both of these examples, the carbon-carbon bonds impart a structure and rigidity that is permanent with regards to human timescales, the films difficult to degrade because of the strong covalent bonds. While the cardanol-derived polymer

represents an effective attempt to develop a functional material, the component chemicals though well used, are not being held to their highest potential. By capitalizing on potential non-covalent interactions, it is wholly possible to design systems for rapid degradation.

2.2 Cardanyl tauramide's equilibrative response

By introducing the aminosulfonic acid taurine into an amphiphilic cardanol system, the nature of the resultant self-assembled system changes [31]. The conditionally essential amino acid taurine facilitates a series of equilibrium processes in mammalian development and imparts similar functionality in micelle, vesicle, and bilayer assemblies of (2) cardanyl tauramide (Fig. 2) [32]. In a 5mM aqueous solution, the CMC value (1.2 mM) cardanyl tauramide was seen to undergo temperature induced phase transformations between exceedingly viscous (solid-like) and free-flowing states. The former was capable of being pulled into thin-string due to an imparted elasticity. The *meta*-substituted phenol was hypothesized to promote self-assembly, aiding cardanol's unsaturated aliphatic chains through π - π stacking [32]. Despite the cohesive non-covalent bonds allowing for molecular recognition, this amphiphilic system undergoes the rapid exchange of amphiphiles in solution to generate thermodynamically stable assemblies at varying temperatures. Similar to homeoviscous alterations in biological lipid systems, cardanyl tauramide responds to external stimuli including shear forces and temperature fluctuations in its attempt to reach a thermodynamic equilibrium. Useful to the materials scientist is that the micelles possess distinctly different physical and chemical properties compared to the vesicles that form in heating the solution 30° above room temperature. To confirm the importance of the unsaturations, John et al. synthesized an all trans conformation of the pentadecylphenol tauramide from which no viscous phase formed [31]. To recreate cardanol's specific lipid mixture in the lab would have been tedious and costly, and yet by using a naturally occurring mixtures, researchers were able to develop highly functional systems as capable as synthetic alternatives. Self-assembled systems can act as reaction centers providing tunable mixing or the storage and release of chemicals. By switching from synthetic to a naturally occurring reagent, the loss of permanence and strength is forgotten in lieu of the possibilities that arise in dynamic systems [33, 34].

2.3 Cardanyl glucoside's sweet and solid gels

Closed-chain sugars are interesting options for an amphiphile's polar moiety because of their non-ionic nature. While ionic surfactants, including the ubiquitous sodium dodecyl sulfate, are widely versatile in aqueous solutions, in looking to assemble structures in both aqueous and organic liquid systems, sugars present as a viable option. Fittingly, they also reprise their role in nature, creating backbones this time for self-assembled fibrillar structures in molecular gels [22, 35]. Cardanol glucoside (3), a 6-O- β -D-glucoside of cardanol, forms strong molecular gels when a 1.0% weight solution in water is heated and cooled to room temperature. Interdigitated hydrophobic alkyl chains congregate behind the sugar moieties, which shield them from the aqueous solvent. Meanwhile in lipophilic solvents, as reversed micelles, the sugar moieties remain shielded from the solvent by their appended aliphatic chains and use hydrogen-bonding to stack into fibers. The cohesive sugar hydrogen bonds, aromatic π - π stacking and aliphatic van der Waals forces allow for spontaneous assembly in organic and aqueous systems, forming helical nanofibers or tubes

in alcohol–water mixtures, and fibrous bundles in organic solvents [36]. Upon further study by increasing the percentage of monoene, pentadecenylphenol glucoside helices transformed into tubular structures, the *cis* kink in the aliphatic chain revealing itself as the key to controlling resultant structures [37]. Gels formed from the assembly of cardanyl glucoside may potentially store other functional chemicals like drugs, physically sequestering them within tunable channels or hollow portions of the high-aspect ratio nanotubes. Despite cardanol's rapid degradation, the dual lipophilic/phenolic nature that makes it a highly versatile chemical also prevents it from being biocompatible, though the incorporation of sugars is a valiant start [39]. By swapping out cardanol's irritating phenol –OH for simple biogenic fatty acids, medicinal and environmental applications arise for the self-assembled networks in solution.

2.4 Multifunctional ascorbic acid amphiphiles

In addition to congregating on their own, self-assembled amphiphile systems possess the ability to act as templates for other assemblies including nanoparticles [38]. By changing the solvent and the amphiphile, two powerful variables arise allowing for tunable templates. As self-assembled systems can produce greatly varied structures depending on the solvent–solute interactions, one could feasibly control the templated structure's architecture by changing the amphiphile, the solvent, or both. Furthermore, as nanoparticles are often synthesized in solution, gels offer themselves as interesting template arenas to control nanostructure uniformity. As synthesis may require numerous components to control size, stability and shape, John et al. thought to combine the function of several synthetic components into one amphiphile: ascorbic acid stearate (4) [39]. While stearic acid is commonly used to stabilize the surface of nanoparticle structures and ascorbic acid is used as an antioxidant, combining the two results in a multi-functional, simplified system. Capable of devoting its distinct ends for separate functions, the amphiphile gains the distinction of template, reducing agent and stabilizing agent, from its synthesis. Employed in a hydrogel solution, ascorbic acid stearate helps afford gold nanoparticles (diameter 16–25 nm). Probing the gel structure with electron microscopy, it seemed to be unaffected by nanoparticle synthesis, a desirable consideration when looking to manufacture nanoparticles. The next step is to vary the structure of the self-assembly, and see the effect on nanoparticle synthesis. Helpfully, the procedure is made easier by the reduction of elements in the synthesis, allowing for a simpler more elegant experiment. Of note is a structurally similar and widely studied gelator, sorbitan monostearate (Span 60), that likely capitalizes on a similar balance of hydro- and lipophilicity to structure oils [40, 41].

2.5 Amygdalin esters and easy drug delivery

Depending on the concentration and structure of the acid reacted with amygdalin, it can break into different combination of products. The natural gentiobiose is readily broken down into two α -glucose units, and either mandelic acid and ammonia, or benzaldehyde and hydrogen cyanide under strong or dilute acid conditions [42]. While controlling the acid concentration is feasible, enzymes represent a way around the potential evolution of hydrocyanic acid. For this reason a lipase solution was used to disassemble and degrade amygdalin laurate (5) fibers capable of gelling organic and aqueous solutions [43]. Fitting was the similar use of biocatalytic enzymes in preparation of the amphiphiles, thus fully

employing two lipases, one to form the ester bond and the other to break it. As the reactivity of these enzymes depends greatly on the nature of the solvent in which they are used, either esterification or hydrolysis can be promoted in non-aqueous or aqueous media, respectively [43]. Researchers demonstrated the conceptual single-step enzyme-triggered drug delivery at physiological conditions using the hydrophobic drug placeholder curcumin [43]. The lipidic nature of the gelator is the key to help disperse the curcumin into its self-assembling hydrogel network, and the biocatalytically cleavable ester bond the key to its release. After a solution of lipase is added, the curcumin separates out with the regenerated amygdalin and lauric acid. Here, the idea goes beyond utilizing specific assemblies using enzymes to carefully disassemble them into targeted products. The next step is making the structuring agent and the drug one and the same.

2.6 Prodrug acetaminophen suberate's hosting assembly

In a recent attempt to combat the cost and time spent developing novel drugs, researchers have begun to teach old drugs new tricks by developing prodrug versions of many bioactive compounds [44]. Many attempts to solubilize small hydrophobic molecules have led to the creation of prodrugs and amphiphiles capable of aiding in this work. Acetaminophen, a synthetic aniline derivative widely used for its antipyretic and analgesic properties, is one of the most popular drugs to combat fever [45]. Acetaminophen suberate (6), a prodrug amphiphile with two separate hydrogen bonding moieties, was synthesized and tested for self-assembly [46]. It was demonstrated that by adding a lipase solution, the hydrogel assemblies of acetaminophen suberate were easily broken and, secondly, the ester bond cleaved, releasing the drug into solution. The weak noncovalent interactions allow for the easy disruption of the self-assembled structures, a pre-requisite to transition from prodrug to drug. After the lipase cleaves the phenol-ester bond, and assembly is no longer possible, suberic acid is left to natural bioprocesses along with the active drug. Researchers took this one step further, again encapsulating the hydrophobic curcumin to demonstrate the dual release of acetaminophen and a second drug via a similar mechanism. The increased lipophilicity of the prodrug serves not only to create structures, but aid in the sequestering of the secondary guest drug until targeted application. The use of bioderived materials is important as the entire system is comprised of biocompatible materials, and materials that undergo chemical conversion in biological systems to release further biocompatible materials. While the prodrug synthesis follows a traditional nonbiocatalyzed procedure (DCC, DMAP, in toluene), the importance of the amphiphile's ability to react via the naturally occurring lipases is of the utmost importance, making them well suited for simple drug delivery systems. While acetaminophen itself is not natural, as natural enzymes may still work with this molecule, the functional product is not hindered by the use of traditional chemical methods, making it a viable component when developing green products.

The past five assemblies represent one side of the highly functional systems, assembled mainly in aqueous solutions. Henceforth, the assemblies will be structured from edible oils and organic solvents earning them the name organogel. As care was taken to note the green nature of the semisynthetic products in the first half, we shall focus on similarly interesting products in the second, but highlight the syntheses and green practices used to create functional smart materials from simple monomers.

2.7 Supergelator trehalose esters

Closed-chain sugars and glycosides represent a library of compounds ripe for selection when choosing a non-ionic hydrophilic amphiphilic moiety. Nature provides a wide array of slightly different sugar structures with varying conformations and chemistries. Despite the prevalence of renewable and natural sugars, they may present as difficult reagents to the skeptic organic chemist because of the numerous hydroxyl groups flanking the heteroatom ring. Many attempts to protect and react sugars have created the wide array of functional sugar esters used as surfactants, yet biocatalysis precludes the need for this as regiospecific catalysts are capable of choosing between primary and secondary alcohols in aqueous or organic media [47]. A variety of highly symmetric sugar diesters, including trehalose acetate (7), were synthesized via heterogeneous biocatalysis with the versatile Novozyme 435 [48]. In addition to selectively synthesizing the diacetate with little or no mono, tri- or polyacylated products, biocatalysis precludes unnecessary protecting groups, lengthy separations, and runs at relatively low temperatures (50°C) [49]. The strength of trehalose ester gels were seen to vary greatly with the length of the alkyl chain, trehalose diacetate producing gels at 0.04wt% in ethyl acetate, an exceedingly low value for a low molecular weight gelator giving it the label supergelator. This ethyl acetate gel is stable with a ratio of one amphiphile to 12 000 solvent molecules. Compared to the ~10–20% wt solutions of polymeric agar used to gel cell cultures, low molecular mass sugar gelators are capable of forming similarly strong soft matter at exceedingly low concentrations, a useful characteristic when looking to use gels as solid reservoirs of liquids. When compared to a chemically acylated trehalose derivative, the mixture of regioisomers gelled solvents at ~10% wt. The advantage of using biocatalysts and natural renewable reagents is compounded of the high yield, regiospecificity, and simple functional product isolation.

2.8 Mannitol dicaprylate's phase-selective gels

A subset of emulsifiers, surfactants that mix immiscible liquid phases, can be found in your pocket. Many personal care and cosmetic products are colored and scented formulations of water, oil, emulsifier, and thickening agent [50]. A unique property of certain hydrophobic amphiphiles is their ability to demonstrate the opposite phenomenon, separating phases by selectively solidifying one [51]. When a saturated alcohol solution of mannitol dicaprylate (8) is introduced to an oil/ water mixture, a solid, easily isolated organogel forms on top of the water [17]. Furthermore when running the experiment with brine to model seawater conditions, the open-chain sugar alcohol derivative gels diesel, gasoline, and crude oil fractions by forming fibers that entangle to entrap the oil. Because molecular organogels are thermoreversible, the oil and phase-selective gelator can be easily recovered by heating and filtration or distillation, a desirable situation should unrefined or refined hydrophobic liquids spill into an aqueous environment. To determine the role of hydrogen bonding, FTIR spectroscopy revealed shifts in the gel's alcoholic hydroxyl groups, which was further confirmed as regularly spaced sugars in the fibers by XRD studies. Fittingly, the chemical contrapositive helps clarify the importance of hydrogen bonds: as sugar alcohol esters are readily soluble in protic solvents, here the rampant hydrogen bonding disorganizes the amphiphiles. Meanwhile in nonpolar solvents, the two hydrophobic chains solubilize the amphiphile and shield hydroxyl groups allowing unperturbed hydrogen bonds to facilitate the assembly into robust fibers. The stereochemistry works in our favor, the alternating

front/back/front/back hydroxyl groups staking nicely; while on the contrary, having just one of the hydroxyl groups switched in sorbitol renders its derivative sorbitol dicaprylate's (9) front/back/back/back assembly yield only partial gels in the same experiments.

2.9 Sorbitol dicaprylate's bittersweet song

Though (9) does not form strong gels like (8), in reviewing its natural components, green synthesis and recent developments, a variety of potential applications present themselves. Sorbitol, an open-chain sugar alcohol is used in food products as a sugar substitute, consumer products as a non-irritating emollient, and in pharmacy as a laxative [52]. Caprylic acid, a medium chain fatty acid, is found in coconut oil and is used as a mild well-spreading component in skin care formulations. The biocatalytic synthesis of sorbitol dicaprylate is one-step, runs at low temperatures with recyclable solvents and is easily worked up via extraction to afford high yields. Additionally, developments removing organic solvents from the reaction flask use technical grade sugars and acids in generating sugar esters under neat conditions, and economic microfluidic flow reactors yield stoichiometric yields at high flow rates [53]. If a majority of the structure is retained by linking hydrophilic heads and lipophilic tails end to end, it seems to show that the phenomena of placing polarized structures in innumerable liquids lends itself to creating smart materials. Perhaps sorbitol dicaprylate's strengths lie in its ability to form weak gels, to thicken and sweeten foods, or as a well-spreading non-irritating emollient. With our senses incredibly discerning the feel and mouthfeel, fragrance, taste, and color of soft matter, only research and time can answer this question. In the meanwhile, the answers we have on how to conduct safe, efficient, and thoughtful research are held within the practices and principles of Green Chemistry and the Biorefinery Model.

3 Summary and outlook

When developing novel soft materials, amphiphiles should remain close at hand because their polarized structure helps create self-assembled systems. Using non-covalent forces to self-organize in solution, these structures are often thermoreversible and easily degraded because an amphiphile's assembly in solution is a physical process compared to chemical reactions in traditional polymer chemistry. To impart functionality to these materials, one may choose to select specific hydrophobic tails and hydrophilic heads with interesting applications, and through experimentation, assess the resultant monomer. As explored, naturally derived reagents present themselves as prime candidates because of their availability, renewability, enzyme- and biocompatibility, and, depending on your selection, safety. By following the basic parameters of the Biorefinery Model and using biocatalysts in the synthesis inherently design novel amphiphiles for degradation into understood and potentially functional compounds. Hereafter, adapting careful design methodologies toward the principles of Green Chemistry, the process may be optimized to create more economic, efficient, and safer reactions.

The future of self-assembled amphiphilic systems lies in the hands of researchers interested and willing to synthesize a wide array of molecules, study their assemblies, and collaborate to develop viable structure–function relationships. In working with soft materials, meaningful names and standardized classifications will develop to explain the subtle

differences between non-covalently bonded organized small molecule systems. Despite the simple nature of two-component soft materials, the complex assemblies, especially those in non-volatile liquids, present as difficult to study via simple electron microscopy and spectroscopic methods. With limitations of current methods such as cryogenic methods that can disrupt and disturb self-assembled architectures, insight into self-assembled systems will grow as new techniques develop to probe dynamic solutions. All in all, the multifunctionality, programmability, and system tunability of self-assembled amphiphilic structures will have them at the forefront of soft materials research in academia and industry for a long while.

While the Biorefinery Model and Green Chemistry principles may be regarded as hindering chemistry and materials research due to what could be deemed somewhat astringent mindfulness, they actually represent viable options for the simultaneous development of novel and potentially safer compounds as well as study of natural processes. As biobased creatures, it is in our best interest to develop safer, more efficient, and economic chemistries, and nature has proven itself a worthy collaborator. Additionally, in using naturally derived monomers the continual study of the relation between structure and function may become much clearer. Perhaps if we look toward nature, and attempt to follow the same reasonable and practical guidelines, there will be no end to the human race.

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Malick Samateh is a Ph.D. candidate currently focused on nanotechnology and materials chemistry at the City University of New York's Graduate Center. He completed his M.S. degree at the City College of New York, studying the design, synthesis, and application of renewable, bio-based amphiphilic molecules used in food and fluid thickening. Currently, he aims to apply bio-based principles toward the design of functional surfactant molecules.

Prof. George John received his Ph.D. from the University of Kerala under the supervision of Dr. C. K. S. Pillai at the National Institute of Interdisciplinary Research and Technology in Trivandrum, India. He completed a year of postdoctoral study at the University of Twente in the Netherlands before continuing onto the Agency for Advanced Industrial Science and Technology (AIST) in Japan. In the fall of 2002, he joined Rensselaer Nanotechnology Center before settling at the City College of New York—CUNY where he is currently a professor of chemistry. His interdisciplinary research focuses on developing value-added chemicals and functional materials from renewable resources using both chemistry and biocatalysis alike.

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Figure 1.
The adapted biorefinery model using natural products as reactants to create materials for society capable of being easily recycled or degraded in a cradle-to-cradle approach.

Figure 2.

Aqueous solutions: (a) Cryo-TEM image of viscous phase cardanyl tauramide vesicles, (b) FE-SEM image of twisted cardanyl glucoside fibers, SEM hydrogel images of (c) acetoaminophen suberate fibers, and (d) ascorbic acid stearate flakes. Organic solutions: (e) trehalose diacetate fibers from an ethyl acetate gel, (f) amygdalin laurate helices from acetonitrile gel, (g) amorphous sorbitol dicaprylate assemblies from toluene gel, and (h) self-assembled mannitol dicaprylate nanofiber aggregates from diesel gel.

Monomers from Renewable Resources

Scheme 1.

Self-assembling monomers from renewably resourced reagents and the non-covalent interaction from which they assemble [54].