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Biomimetic Design and Performance of Polymerizable Lipids

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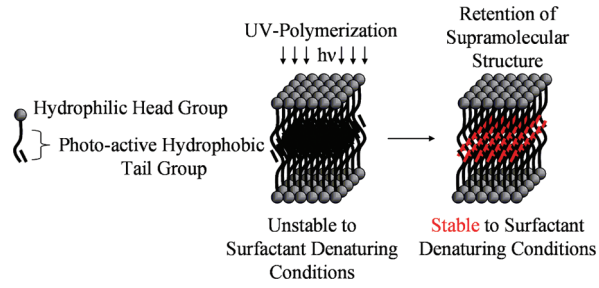

Bilayer lipid membranes (BLMs) have received significant attention over the past several decades because of their applications in biological and material sciences. BLMs consist of two amphiphilic lipid layers arranged with their hydrophilic head region exposed to the surrounding aqueous environment and hydrophobic domains in the core. In biology, lipid membranes confine and support the cell structure while selectively controlling the diffusion of ions and proteins between the intra- and extracellular matrix (ECM). Naturally derived lipid monomers spontaneously self-assemble to develop smart gateways that recognize and incorporate desired protein transporters or ion channels. BLMs are useful research models of lamellar lipid assemblies and associated protein receptors in cell membranes. The transport properties of lipid membranes can be tuned through careful consideration of the solution medium, transporter functionality, and pH, as well as other environmental conditions. BLMs are of particular interest in the design of biofunctional coatings, controlled release technologies, and biosensors; however, high-performance applications require lipid membranes to remain stable under harsh denaturing conditions. Accordingly, synthetic strategies are often proposed to increase the chemical and mechanical stability of lipid assemblies.

The polymerization of self-assembled lipid structures is a strategy that results in robust biocompatible architectures, and diverse reactive functional groups are available for the synthesis of monomeric lipids. The selection of the polymerizable functionality and its precise location within the lipid assembly influences the ultimate supramolecular microstructure and polymerization efficiency. The biomimetic potential of polymerized lipids depends on the stability and robustness of the self-assembled membranes, and it is essential that the polymerizable functionality not disturb the amphiphilic nature of the lipid to maintain biocompatibility.

Innovative applications are the motivational force for the development of durable polylipid compositions. Surface modification with biocompatible polylipids provides the opportunity for specific binding of biological molecules for applications as sensors or controlled release delivery vehicles. The ability to create stable lipid assemblies requires a comprehensive understanding of the mechanism of lipid polymerization in confined supramolecular geometries. The future is exciting as researchers begin to fully understand the morphology of polylipids in an effort to successfully produce naturally derived sustainable materials. In this Account, we highlight recent efforts to covalently stabilize lipid membranes and discuss emerging applications of mechanically robust self-assembled lipid architectures.

Introduction

Self-assembled lipid membranes and coatings offer potential as biosensors, controlled release vehicles, and biofunctional coatings due to their selective permeability and biomimetic properties. Polymerizing lipid assemblies is a strategy used to produce mechanically durable biocompatible architectures, and the choice of the polymerizable functionality influences the self-assembled lipid microstructure and polymerization kinetics. It is important that the polymerizable group not disturb the spontaneous self-assembly of the lipid architecture in order to retain the biomimetic

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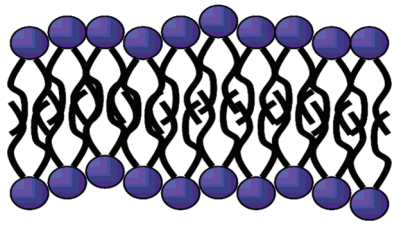

FIGURE 1. Bilayer lipid membrane (BLM).

potential of polymerized lipids. The application of polylipids requires a comprehensive understanding of the lipid polymerization mechanism in confined supramolecular geometries and the influence of polymerization on the lipid membrane's interaction with proteins and other biological guests. Innovative controlled release, filtration technologies, and biofunctional coating applications are the motivational force for the enhancement of durable polylipid compositions, and the outlook is exciting as researchers begin to fully comprehend the transitions and morphologies of polylipids in an effort to successfully produce naturally derived sustainable materials. In this Account, exciting recent efforts to covalently stabilize lipid membranes and emerging applications of mechanically robust self-assembled lipid architectures are highlighted.

Origin and Self-Assembly of Lipid Membranes

Supported lipid membranes or bilayer lipid membranes (BLMs) have received significant attention over the past several decades due to their potential application in biological and material sciences.[1−4] Biological lipid membranes confine and support the cell structure while selectively controlling the diffusion of ions and proteins between the intra- and extracellular matrix (ECM).[5] Research interest focuses on using BLMs as models of the lamellar assembly of lipids, as shown in Figure 1, and associated protein receptors in cell membranes.[6−9] Common procedures for the assembly of BLMs include using either Langmuir−Blodgett−Schaefer (LBS) or vesicle fusion techniques.[6−8,10] LBS deposition techniques provide precise control over the packing density and composition of the film. Depending upon lipid composition and experimental conditions, LBS techniques allow for control over the lateral organization and membrane asymmetry.[11] Vesicle fusion techniques are advantageous due to their more straightforward deposition procedure.[12] However, vesicle fusion techniques only form bilayers from fluid-phase lipids, limiting control of bilayer symmetry and organization.[13]

Amphiphilic lipids are composed of one or more hydrophobic chains covalently linked to a hydrophilic head. Glycerolipids and phospholipids are biologically derived lipids that contain a glycerol group linking the hydrophobic and hydrophilic segments.[14] Unfavorable enthalpic interaction of the hydrophobic tails with the polar medium drives the self-assembly of lipids in aqueous environments and leads to the spontaneous aggregation of hydrophilic and hydrophobic domains.[15] Self-assembled hydrated lipids are physiochemically, not covalently, bonded, and the lipids laterally diffuse in the bilayer with their polar heads oriented at the aqueous interface and hydrophobic tails retained in the core of the aggregate. The supramolecular phase of hydrated lipids is dependent upon concentration, temperature, pH, and pressure, in addition to the lipid chemical composition, which determines the spontaneous curvature at the lipid−water interface.[16]

In biomedical applications as biosensors or in controlled release technologies, assembled membranes have not typically demonstrated sufficient mechanical strength.[17] Researchers have incorporated sugars, cholesterol, and proteins into BLMs in an attempt to increase their mechanical stability.[18−22] These additives have not provided sufficient mechanical strength for future applications that require BLMs to survive a range of pressures, temperatures, or harsh chemical conditions. Rangelov and researchers[23,24] sterically stabilized phosphatidylcholine (PC) liposomes by coating PC vesicles with poly(ethylene glycol) (PEG). PEG was anionically copolymerized with 1−4 repeat units of a lipid monomer, 1,3-didodecyloxy-2-glycidyl-glycerol (DDGG), to produce copolymers with molecular weights between 6000 and 8000 g/mol. The lipid monomer contained didodecyl hydrocarbon tails that were covalently attached to an epoxide polymerizable head. In aqueous media, the hydrocarbon chains of the lipid repeat unit self-assembled into the hydrophobic regions of PC liposomes, anchoring PEG to the phospholipid bilayer, as shown in Figure 2. Immobilized PEG formed a polymeric coating around the PC liposomes, which inhibited the adsorption of denaturing proteins. Protection from disruptive proteins is critical for polymer−lipid sterically stabilized liposomes to function as drug delivery vehicles.[25,26]

In order to exploit the biomimetic properties of BLMs, strategies for bilayer stabilization are required that do not coat the lipid membrane, which disrupts desirable associations with the bilayer surface. The polymerization of lipid bilayers represents a convenient strategy to increase BLM stability, and consequently, the polymerization of lipid membranes has received significant interest since the early 1980s.[27−29] Diverse synthetic strategies afford the opportunity to incorporate polymerizable functionalities in the head, chain, or tail region of the lipid. Researchers have functionalized lipids with acrylic,[30,31] styrenic,[32] acetylene,[33−35] and dienoyl[36−39]

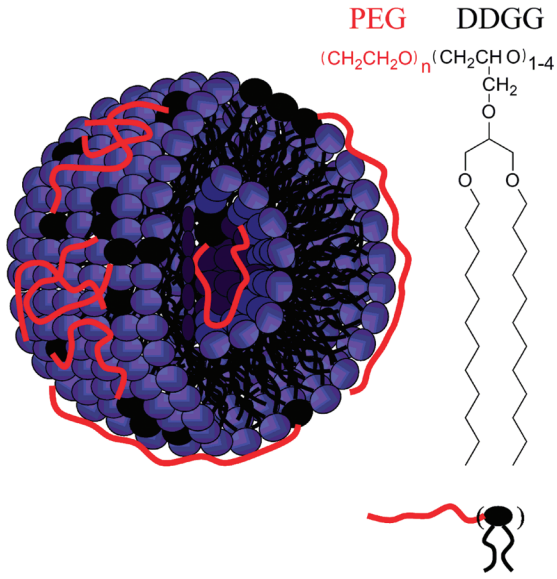

FIGURE 2. Phosphatidylcholine (PC) vesicle sterically stabilized with PEG–DDGG copolymer.

groups. As expected, the location and chemical functionality of the polymerizable group influences the supramolecular structure and polymerization efficiency of monomeric lipids. The polymerizable functionality must not disturb the amphiphilic nature of the lipid to maintain self-assembly, since the biomimetic potential of polymerized lipids depends on the stability and robustness of the self-assembled membranes. Rossi and Chopineau[40] recently published a review on the biomimetic properties of tethered lipid membranes. Tethered lipid membranes are anchored to a supporting solid surface, and a polymeric coating, receptor/ligand spacer lipid, or functionalized monolayer insulates the lipid from the substrate. Lipid membranes that are tethered to a solid surface provide the opportunity to model and efficiently characterize the interaction of proteins with lipid membranes. Since lipid monomers are not covalently connected to form a polylipid, tethered membranes will not be discussed in this Account, and readers are referred to Rossi and Chopineau's review of tethered lipid membranes.

Polymerizable Hydrophobic Regions in Lipid Membranes

Recently, reactive BLMs have received interest for the generation of micropatterned membranes.[41,42] Morigaki and researchers[41] investigated the stability of photopolymerized lipid bilayers for the lithographic construction of micropatterned biomimetic membranes. The researchers compared the photopolymerization properties of two diacetylenic phospholipids on quartz and oxidized substrates. The fluorescence and strong UV–vis absorption properties of polyeneynes facilitated characterization using UV–vis absorption and fluorescence spectroscopy. The diacetylenes differed in their composition and degree of functionality, as shown in Figure 3. Lipid **1** was a diacetylene containing monoalkyl phosphate, phosphoric acid monohexacosa-10,12-diynyl ester, and lipid **2** was a bis-diacetylene dialkyl phospholipid, 1,2-bis(10,12-tricosadiynoyl)-*sn*-glycero-3-phosphocholine. The two lipid monomers displayed significantly different photoreactivities.

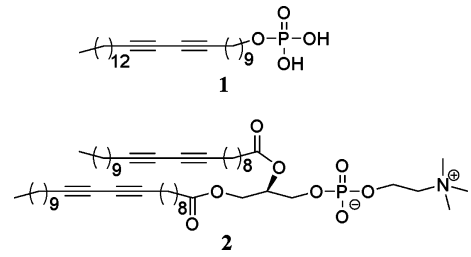

FIGURE 3. Diacetylene monoalkyl phosphate (**1**) and bis-diacetylene phospholipid (DiynePC) (**2**).

The monoalkyl phosphate lipid photopolymerized at a remarkably faster rate than the dialkyl phospholipid and achieved a higher degree of polymerization. The higher rate and degree of polymerization of **1** was attributed to the efficient packing ability of the monoalkyl amphiphile compared with the dialkyl. Thus, photopolymerization behavior of diacetylenes strongly depends on the molecular packing capabilities. In addition, photopolymerized emission spectra of the amphiphiles displayed substrate dependence. The photopolymerization of **1** on oxidized silicon and quartz displayed the emission of both red and blue polymers. However, the photopolymerization on oxidized silicon displayed a stronger blue emission than on quartz. The polymerization efficiency of diacetylene lipids depends on the packing capability and mobility of assembled lipid membranes. Increased interaction between the lipid and substrate can inhibit the lipid chain rearrangement within the bilayer leaflet and encumber the polymerization of diacetylene lipids.[43] Lipid chain reconfirmations are necessary to fulfill the topochemical requirements for diacetylene lipid polymerization. The authors suggested that the increased hydrophilicity of the quartz substrate compared with the oxidized silicon produced a less tightly packed arrangement of diacetylene lipids decreasing the polymerization efficiency and resulting in a larger portion of red-emitting polyeneyne on quartz. However, another possibility for the decreased polymerization of lipid **1** on quartz could be attributed to the formation of hydrogen bonds between the lipid **1** headgroup and the quartz surface, which limits the freedom of the lipid chains to rearrange and satisfy the diacetylene topochemical polymerization requirements.

The influence of substrate on the photopolymerization behavior of lipid **2** was less pronounced, and **2** produced only

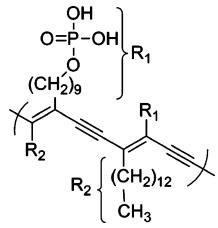

FIGURE 4. Linear π-conjugated polydiacetylene backbone of **1**.

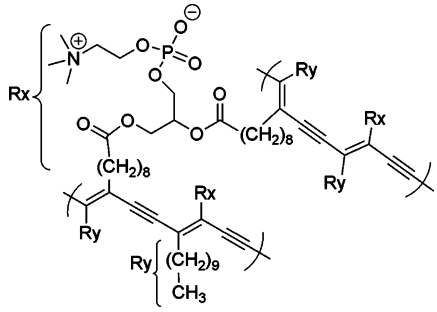

FIGURE 5. Cross-linked π-conjugated polydiacetylene network of **2**.

red-emitting polymers on both quartz and oxidized silicon; however, photopolymerization of lipid **2** on oxidized silicon produced a shorter conjugated polyeneyne chain compared with that on quartz. The increased degree of polymerization on quartz could have resulted from the decreased packing capabilities of lipid **2** on oxidized silicon, or the less hydrophilic oxidized silicon surface could have promoted intermolecular zwitterionic associations of lipid **2** headgroups. The zwitterionic associations could have limited the mobility of the diacetylene lipid chains to rearrange and fulfill the spatial requirements necessary to achieve diacetylene polymerization.

The difference in polymer backbone configuration distinguished between red and blue emission spectra, and upon UV-polymerization, the polydiacetylenes emitted blue light. The polymer shifted to red emissions when the polyeneyne chain length became long enough for the polymer chain to coil-up due to the increased chain mobility provided in the polymer backbone. The emission remained blue if sufficient intermolecular interactions were present to maintain an extended chain. Polymers **1** and **2** were expected to red shift if the amphiphiles were not sufficiently packed on the given substrate.[44] For quartz and oxidized silicon substrates, **2** displayed a higher amount of red emission than **1**.

Figure 4 displays the resulting π-conjugated polydiacetylene of **1**, and Figure 5 shows the network formation of **2**. Diacetylenes can polymerize in a 1,4-addition mechanism that produces a π-conjugated polymer backbone. The polymerization of diacetylenes requires confined spatial requirements of the monomer units due to the topochemical nature of diacetylene chain addition.[45] Due to the network formation of the bis-diacetylene, lipid **2** resulted in more mechanically robust

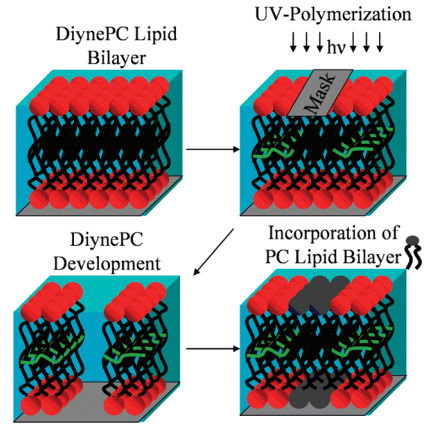

FIGURE 6. Lithographically micropatterned fluid lipid bilayers.[46]

bilayers compared with **1**. Polymerized bilayers of **2** did not dissolve in organic solvents and were resistant to surfactant treatment, and in contrast, polymerized bilayers of **1** readily dissolved in water. The increase in stability of **2** was attributed to the higher degree of photoactive functionality that more efficiently produced a cross-linked structure. The mechanical stability of **2** was sufficient to endure the mechanical stress of lithography; however, the packing difficulties prevented the formation of domain boundaries with sharp features.

Morigaki and co-workers[46] also formed micropatterned lipid membranes containing polymerized and fluid lipid bilayers on glass substrates. Bilayers of **2** were lithographically photopolymerized on solid substrates, and masks over the substrate produced a patterned surface after the nonirradiated portions were developed, as Figure 6 depicts. Phosphocholine (PC) fluid lipid bilayers were incorporated into the developed portions of the substrate from the fusion and reorganization of suspended small unilamellar PC vesicles. The dosage of UV-irradiation controlled the lateral diffusion of the fluid lipid layer, and high UV dosages produced polymerized bilayers that were impermeable to fluid bilayers. Higher degrees of DiynePC polymerization confined fluid bilayers to defined areas, and lower UV dosages allowed fluid bilayers to laterally diffuse into polymerized lipid domains.

Polymerizable Hydrophilic Regions in Lipid Membranes

The photopolymerization of diacetylene groups to stabilize BLMs is a mature field. The topotactic nature of diacetylene-lipid photopolymerization requires efficient chain packing to produce sufficient molecular weights for increased stability.[47] Lipid diffusion in the fluid phase prevents diacetylenelipids from achieving high degrees of polymerization. Ramakrishnan et al.[48] synthesized counterion polymerizable lipids, as

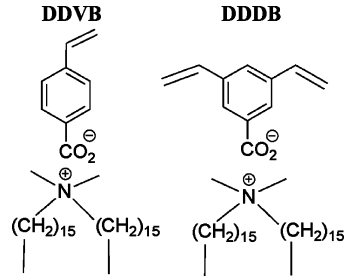

FIGURE 7. Dicetyldimethylammonium-4-vinyl benzoate (DDVB) and dicetyldimethylammonium-3,5-divinyl benzoate (DDDB).

shown in Figure 7, containing reactive vinyl groups to increase the applicability of polylipids. Dicetyldimethylammonium-4-vinyl benzoate (DDVB) was synthesized from dicetyldimethylammonium hydroxide (DDAH) and 4-vinyl benzoic acid, and dicetyldimethylammonium-3,5-divinyl benzoate (DDDB) was synthesized from DDAH and 3,5-divinyl benzoic acid. Sonication of solvated lipids resulted in single lamellar vesicle dispersions, and exposure to UV light in the presence of an oil-soluble photoinitiator, 2,2-dimethoxy-2-phenyl acetophenone (DMPA), initiated vesicle polymerization. Vesicular polymerization of DDVB and DDDB resulted in linear and cross-linked polylipids, respectively. The vinyl functionality was not covalently bonded to the lipid; however, the vinyl groups were electrostatically associated with the lipid polar head. Polymerization of the liposomes counterion shell provided a durable coating around the lipid bilayer, and the bilayer components retained their monomeric state due to their noncovalent interaction. DMPA was used as the photoinitiator for both DDVB and DDDB vesicle polymerizations and proved more efficient than water-soluble photoinitiators.

Cetyl trimethylammonium bromide (CTAB) was incrementally added to determine the vesicle stability to lysis, and vesicular light scattering intensity was monitored as a function of CTAB concentration. The scattering intensity of nonpolymerized and DDVB polyvesicles decreased significantly upon the addition of 2 equiv of CTAB. However, the scattering intensity of DDDB cross-linked vesicles decreased only 10% with the addition of 2 equiv of CTAB. The small decrease in scattering intensity indicated that the multifunctional lipids produced a more stable vesicle. The researchers examined the stability of vesicles in organic solvents. The light scattering intensity of nonpolymerized DDVB and DDDB vesicles continuously decreased due to dissolution of vesicles in ethanol. Linear polymerized DDVB vesicles proved more stable than nonpolymerized vesicles. Linear polymerized vesicle scattering intensities sharply increased with increasing ethanol content, until the vesicles precipitated. The scattering intensity of DDDB cross-linked vesicles increased marginally, and precipitation did not occur. The researchers' speculated that the cross-linked rigid network prevented lipid chain reorganization and the semirigid cross-linked vesicles did not aggregate and remained suspended in solution.

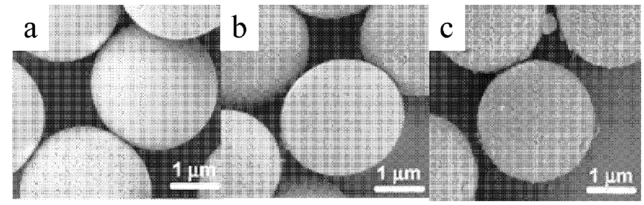

FIGURE 8. (a) MF particle, (b) PE multilayer-coated MF particle, and (c) Si-lipid polysiloxane-coated PE-multilayer MF particle.[49]

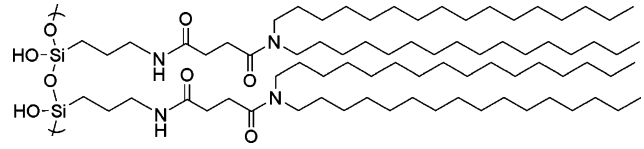

FIGURE 9. Polysiloxane silane-lipid that was deposited onto PE-coated monodisperse colloidal particles.

Katagiri and Caruso[49] developed robust organoalkoxysilane-based lipid (silane-lipid) coatings on monodisperse colloidal particles. Layer-by-layer (LbL) deposition techniques were used to alternately deposit layers of positively charged poly(diallyldimethylammonium chloride) (PDDA) and negatively charged poly(sodium 4-styrenesulfonate) (PSS) onto a colloidal template. Electrostatic interactions facilitated the silane-lipid deposition onto the polyelectrolyte (PE) multilayer-coated colloidal particles. SEM images of the uncoated melamine formaldehyde (MF) template particles (a), PE multilayer-coated MF particles (b), and silane-lipid coated PE multilayer-coated MF particles (c) are displayed in Figure 8. Acidic treatment of the lipid-coated particle resulted in the dissolution of the MF core, resulting in hollow lipid-coated PE capsules. The alkoxy silane functionalized silane-lipid was pretreated with acid to catalyze the silyl hydrolysis and form the polysiloxane, as shown in Figure 9. The silane-lipid produced a stable polysiloxane that was highly resistant to surfactant and ethanol denaturing solutions. The stability of the silane-lipid coating was compared with PE multilayer-coated colloidal particles coated with a nonpolymerizable lipid, dimyristoylphosphatidic acid sodium salt (DMPA). Fluorescence measurements indicated that even low surfactant or ethanol concentrations resulted in the decoating of DMPA membranes from the particle surface. The increased silane-lipid stability was attributed to the polysiloxane network.

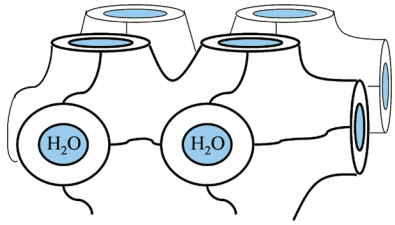

FIGURE 10. Lipid bicontinuous cubic liquid-crystalline phase.

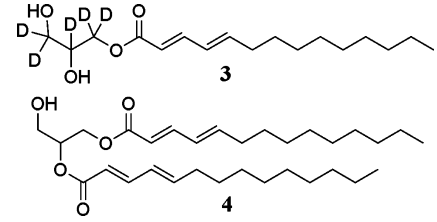

FIGURE 11. Polymerizable monoacylglycerol (**3**) and cross-linkable 1,2-diacylglycerol (**4**).

Polymerization of Nonlamellar Lipid-Cubic Phases

Hydrated lipids also form liquid-crystalline phases depending on their structural composition and concentration.[50] Marder and co-workers published a review describing cubic liquid-crystalline nanoparticles and discussed their potential application as drug delivery vehicles.[51] Lipid cubic phases form optically isotropic gels with extremely high surface areas and are comparable to inorganic zeolites.[52] Lipid bilayers in cubic liquid-crystalline phases form continuous, three-dimensional cubic-lattice structures in water, as shown in Figure 10.[53] Lipid cubic phases are dependent upon their environmental conditions and only form bicontinuous phases within a narrow range of temperatures, pressures, and lipid concentrations.[54] The hydrophilic and hydrophobic continuous domains of lipid cubic phases solubilize lipophilic, hydrophilic, or amphiphilic compounds, making the three-dimensional structures ideal for controlled release drug delivery and separation technologies.[55,56] Other applications of lipid cubic phases include templates for the synthesis of nanomaterials[57,58] and encapsulation of active reagents in cosmetics and packaging technologies.[59,60]

Due to the limited temperature and concentration ranges for the formation of lipid cubic phases, a strategy is necessary to increase the stability and application range of liquid-crystalline lipid structures. Stabilization of the cubic phase generates a bicontinuous phase with interpenetrating water channels. Typical aqueous channels in inverted liquid-crystalline lipid phases vary from 3 to 20 nm in diameter depending upon the lipid composition and environmental conditions.[61,62] Functionalization of the channel surface with chemical host or labels provides a strategy to anchor biological guests or perform separations within the high surface area channeled networks.[63−66]

Polymerization of reactive lipids in cubic phases offers a strategy to stabilize lipid liquid-crystalline phases. Thermal, photochemical, or redox initiation mechanisms are efficient strategies for the stabilization of cubic phases.[61,67] Gin, Noble, and co-workers recently published a review describing the polymerization and cross-linking of nonlamellar phases with retention of their microstructure.[68] The review discussed the application of polymerized lyotropic liquid-crystalline (LLC) microstructures in the design of novel membrane technologies. Gin and co-workers have tailored the polymerized LLC nanochanneled networks through careful consideration of the lipid composition and environmental conditions to develop robust cubic phases ideal for nanofiltration membranes,[69] gas separation membranes,[70] breathable vapor-resistant membranes,[71] and water desalination technologies.[72] Gin et al. also wrote an earlier review describing the catalytic activity of LLC phases developed from amphiphiles containing photoactive acrylic groups at the termini of the hydrophobic chains.[52] Sulfonic acid groups were incorporated in the hydrophilic head portions of the polymerizable amphiphiles, which under optimized conditions formed reverse hexagonal phases (H_{II}). Cross-linking the H_{II} microstructures produced robust ordered networks that acid-catalyzed esterification reactions at a higher rate and produced less byproduct than commercially available nonordered sulfonic acid resins.

O'Brien and co-workers synthesized polymerizable monoacylglycerol-d_5 (**3**) and cross-linkable 1,2-diacylglycerol (**4**) lipids, as shown in Figure 11.[73] The monoacylglycerol lipid was deuterated to assist in the NMR characterization of the phase behavior. NMR, along with cross-polarized optical and X-ray diffraction characterization, confirmed the formation of an isotropic optically clear lipid cubic phase for a **3**/**4** (9:1 molar ratio) mixture in water between 5 and 45 °C. Free radical polymerization of the lipid mixture at 45 °C produced a polylipid that was soluble in organic solvents and remained optically clear. The polymerization achieved a high conversion of the dienoate groups as determined with UV−vis spectroscopy and a M_n of 5×10^4 g/mol with a degree of polymerization of approximately 200 was determined using size exclusion chromatography with dichloromethane as the mobile phase. The isotropic nature of the polymerized bicontinuous cubic phase was confirmed with cross-polarized light and X-ray diffraction. The polymerized lipid-cubic phase was thermally stable up to 70 °C, compared with only 45 °C for the cubic phase of the nonpolymerized lipid mixture.

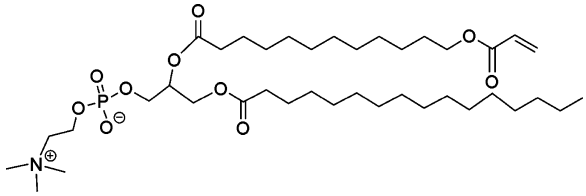

FIGURE 12. 1-Palmitoyl-2-[1,2-(acryloyloxy)dodecanoyl]-*sn*-glycero-3-phosphocholine (ARPC).

Marder, O'Brien, and co-workers examined the inverted bicontinuous cubic phase photo-cross-linking of 3-(2,4,13-(*E*,*E*)-tetradecatrienoyl)-*sn*-glycerol (**5**).[74] The acylglycerol lipid was mixed with a hydrophobic cross-linking monomer, divinyl benzene (DVB). A 9:1 (**5**/DVB) molar ratio at 25 wt % in water produced an isotropic clear cubic gel that was thermally stable to 45 °C. In the aqueous environment, DVB was internalized into the cubic phase hydrophobic domain containing the polymerizable tetradecatrienoyl tail. The cubic phase was dispersed into cubosomes in the presence of polymeric dispersing agents, and the cubosomes were subsequently photo- and redox-polymerized producing stabilized bicontinuous cubic nanoparticles. Cross-linked cubosomes provide promising bicontinuous cubic phases for applications that require exposure to severe conditions.[51]

Characterizing the Efficiency of Lipid Membrane Polymerization

Morphological characterization of lipid assemblies is typically performed with X-ray diffraction, NMR spectroscopy, differential scanning calorimetry, and transmission and scanning electron microscopy.[75] Characterization of polymerized lipid layers is often difficult and traditional polymer characterization techniques are not applicable for immobilized lipid membranes. Evaluating the degree of polymerization is desirable to determine the efficiency of initiation and to establish structure−property relationships. Dluhy et al.[76] utilized near-IR Raman spectroscopy to characterize the photopolymerization of 1-palmitoyl-2-[1,2-(acryloyloxy)dodeca-noyl]-*sn*-glycero-3-phosphocholine (ARPC), which was designed to increase the mechanical integrity of lipid films for biological coatings on polymeric membrane-mimetic films and vascular grafts. ARPC contained a photoreactive acrylate group at the terminus of one hydrocarbon chain, as shown in Figure 12. The researchers formed model lipid films from the white-light irradiation of hydrated ARPC vesicles using eosin Y (EY) as the photoinitiator and compared the degree of polymerization as determined from IR and near-IR Raman spectroscopy. IR is the standard method to determine the degree of polymerization; however, IR characterization of lipid films on polyelectrolyte multilayers (PEMs) is difficult due to the relatively weak C=C vibration on multicomponent substrates. Near-IR Raman spectroscopy provides better analysis of homonuclear C=C stretching vibrations in a multicomponent system. The difference in the degree of polymerization between the two methods was less than 0.7% and indicated that near-IR Raman spectroscopy was the preferred characterization method to determine the extent of polymerization on multicomponent substrates. The researchers subsequently used in situ near-IR Raman microscopy to characterize the formation of lipid membrane films on vascular grafts from the photopolymerization of ARPC films on PEMs immobilized on the luminal surface of vascular polytetrafluoroethylene (PTFE) grafts, as shown in Figure 13. The lipid-coated graft was irradiated with 514.5 nm light for periods up to 300 s, and near-IR Raman microscopy determined the efficiency of polymerization. Photopolymerization produced a stabilized lipid-coated PTFE vascular graft.

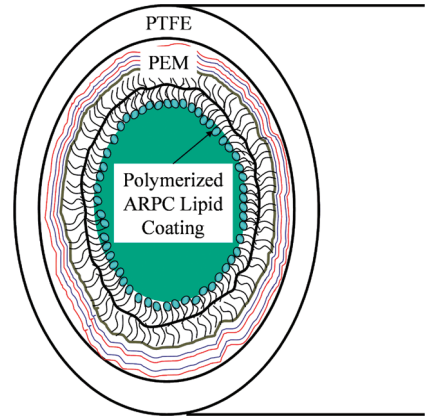

FIGURE 13. Luminal surface of PTFE vascular graft coated with PEM and ARPC polylipid.

Biomimetic Properties of Polymerized Lipids

Retention of biomimetic properties remains essential following lipid polymerization. Extensive cross-linking or high molecular weight polylipid membranes can negatively affect the activity of incorporated proteins or transporters, and irradiation can potentially deactivate encapsulated biological molecules. Saavedra and co-workers investigated the activity of bovine rhodopsin (Rho) integrated into a UV-polymerized lipid bilayer.[77] The lipid bilayer consisted of 1,2-bis[10-(2′,4′-hexadienoyloxy)decanoyl]-*sn*-glycero-3-phosphocholine (bis-SorbPC), as shown in Figure 14, which formed a cross-linked network due to the dienoyl functionality of both hydrocarbon chains. Photopolymerization of bis-SorbPC was initiated with exposure to UVA irradiation and did not require a photoinitiator. The propagating mechanism of bis-SorbPC proceeds from the photoactivated interaction of sorbyl monomer units or the formation of diradicals generated from the pho-

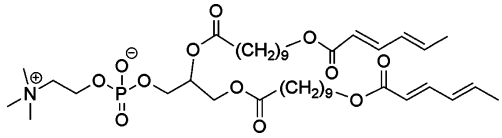

FIGURE 14. 1,2-Bis[10-(2′,4′-hexadienoyloxy)decanoyl]-*sn*-glycero-3-phosphocholine (bis-SorbPC).

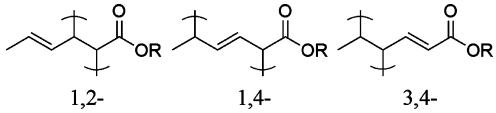

FIGURE 15. The 1,2-, 1,4-, and 3,4-diene addition products of dienoyl polymerization.

toexcited singlet state.[78] A combination of 1,2-, 1,4-, and 3,4-additions of the diene are generated during the radical polymerization of bis-SorbPC, as shown in Figure 15. The degree of polymerization is lower when photoinitiation occurs at temperatures above the main phase transition, T_m.

Visible light activated the visual photoreceptor Rho. Plasmon waveguide resonance (PWR) spectroscopy, which detects the optical properties of thin films, monitored Rho during and after bis-SorbPC polymerization. The lipid bilayer was formed over the resonator surface of the PWR in an aqueous solution, and aliquots of Rho in octylglucoside were introduced to the lipid bilayer formed in the PWR cell. UV-light initiated polymerization through a port in the PWR cell. After photopolymerization, the Rho−lipid bilayer structure was exposed to yellow light and monitored using PWR.

Photopolymerization of the lipid bilayer produced a cross-linked structure that was stable in the presence of surfactants, and greater than 95% conversion of the lipid monomer was achieved. Characterization of the Rho−lipid bilayer structure during exposure to yellow light indicated that Rho was still photoactive in the polylipid bilayer. The photoactivity of Rho incorporated in the polymerized lipid bilayer was compared with Rho incorporated in a nonpolymerized lipid bilayer, and comparable photoactivities were obtained. The researchers concluded that the cross-linking of bis-dienoyl phospholipid bilayers did not affect the photoactivity of Rho.

To protect fluorescent tags from unfavorable protein adsorption, Saavedra and researchers[79] coated the probes with a cross-linked polylipid coating. Rhodamine−protamine dye molecules were encapsulated in silica nanoparticles (Si NPs, 65−100 nm), and the luminescent Si NPs were coated with cross-linkable bis-SorbPC. Tagged Si NPs are used a fluorescent probes to label cultured cells; however, the silica surface is prone to nonregulated binding in biological media, and the lipid coating was implemented to regulate interactions with the fluorescent Si NPs surface. The lipid coating was photopolymerized achieving 95% monomer conversion, producing a chemically cross-linked polylipid coating that protected the luminescent Si NPs from undesired associations. The nonspecific binding to HeLa cells in the presence of surfactants for Si NPs coated with cross-linked bis-SorbPC was compared with Si NPs coated with a nonpolymerizable lipid, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC). Before introduction of the surfactant, both lipid coatings limited NP interaction with the HeLa cells; however, in the presence of a denaturing surfactant, the DOPC bilayers delaminated from the particle surfaces, resulting in bare Si NPs, which adsorbed to the cells surface. The cross-linked bis-SorbPC coating prevented the adsorption of Si NPs to HeLa cells in the presence of surfactants, proving the stability of the polylipid coating. Retention of the phospholipid bioactivity was demonstrated when biotin was incorporated into the polylipid layer coated on the Si NPs, and biotin-functionalized NPs successfully targeted the conjugation to protein receptors.

Perspective

There are several methods used to increase the stability of lipid assemblies. Polymerization of lipid structures is a strategy used to produce robust biocompatible architectures. There are a wide variety of chemical functionalities available for the synthesis of monomeric lipids. The polymerizable functionality and location within the lipid structure determine the supramolecular microstructure and polymerization efficiency. Lipid monomer conversions of greater than 95% were observed under optimal conditions.[77,79] Applicability of stable lipid assemblies requires a comprehensive understanding of the lipid polymerization mechanism in confined supramolecular geometries and defects within the self-assembled architectures. Surface modification with biocompatible polylipids provides the opportunity for specific binding of biological molecules for applications as sensors, as controlled release delivery vehicles, or in the development of biologically compatible devices. Control of the polymerization kinetics, low monomer conversion, and delamination of the polylipid coating from the substrate are several limitations in the design of polylipid functional materials that future investigations will need to address.

The future is exciting as researchers begin to fully understand the morphology of polylipids in efforts to successfully produce sustainable materials. Innovative applications are the motivational force for the development of novel lipid compositions. Our group has electrospun nonwoven lipid membranes from lecithin solutions to produce high surface area, biocompatible membranes with fibers as small as 2.8 μm.[80] Above the entanglement concentration (C_e), the lipid worm-

like micelles formed entangled couplings similar to polymer coils. Lipid wormlike micelles have contour lengths on the micrometer scale.[81] They are flexible, cylindrical rods that display viscoelastic properties in solution. Our current efforts are focused on the in situ UV-curing of electrospun fibers of soy-based lipids for the generation of sustainable biocompatible membranes and robust protective glycerol coatings. In-situ UV curing during electrospinning is a novel process for the development of electrospun lipid membranes with mechanical integrity and provides environmentally beneficial processing conditions.

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Timothy E. Long earned his Ph.D. in chemistry under the direction of Prof. James E. McGrath at Virginia Tech in 1988 and upon graduation, immediately joined the Corporate Research Laboratories at Eastman Kodak Company. He subsequently joined Eastman Chemical Company in 1993 in Kingsport, Tennessee, prior to joining the faculty at Virginia Tech in 1998. He is currently a Professor in the Department of Chemistry at Virginia Tech and manages an international research group dealing with diverse areas of macromolecular science and engineering.

FOOTNOTES

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