

a representative exchangeable apolipoprotein, apoLpIII from *Locusta migratoria*, using surface-sensitive X-ray techniques. This model exchangeable apolipoprotein contains a 5-helix bundle and shows high structural homology to the 4-helix bundle in the N-terminus of apoE, a major mammalian exchangeable apolipoprotein. We found that the structure of two diacylglycerols, the proposed binding partner of apoLpIII, dioleoylglycerol (DOG) and 1-palmitoyl, 2-oleoylglycerol (POG), showed great resemblance to other (phospho)lipid monolayers except for details due to differences in the headgroup region. Despite their near identical chemical structures small differences in organization as monolayers were observed between DOG and POG. For the pure apoLpIII monolayer we observed that the unfolded protein was best represented by two distinct regions. This surprising result may originate from the high degree of glycosylation of apoLpIII. The interaction of apoLpIII underneath a densely packed diacylglycerol monolayer causes the surface pressure to increase rapidly. The analysis of the X-ray reflectivity of the lipid/protein system, right after the injection of apoLpIII, shows a diffuse layer underneath the lipid monolayer due to the binding and unfolding of apoLpIII. This may be the first direct visualization of the dynamic unfolding of an exchangeable apolipoprotein at a lipid interface. Our data suggest that the initial interaction occurs when the protein is tilted with respect to the lipid monolayer, a process that would favor the opening of the helix bundle.

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Folding of Lipid Monolayers Containing Lung Surfactant Proteins SP-B1-25 and SP-C Studied via Coarse-grained Molecular Dynamics Simulations

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To explore the role of lung surfactant proteins SP-B and SP-C in storing and redelivering lipid from lipid monolayers during the compression and re-expansion occurring in lungs during breathing, we simulate the folding of lipid monolayers with and without these proteins. We utilize the recently developed MARTINI coarse-grained force field to simulate monolayers containing pure dipalmitoylphosphatidylcholine (DPPC) and DPPC mixed with palmitoyloleoylphosphatidylglycerol (POPG), palmitic acid (PA), and/or peptides. The peptides considered include the 25-residue N-terminal fragment of SP-B (SP-B₁₋₂₅), SP-C, and several SP-B₁₋₂₅ mutants in which charged and hydrophilic residues are replaced by hydrophobic ones, or vice versa. Most of these peptides facilitate folding of the monolayer during compression by a “zipper” mechanism, which is dependent on the formation of a peptide aggregate. However, we find that if the number of hydrophobic residues is decreased significantly monolayer folding does not occur via the “zipper” mechanism. During the re-expansion of folds formed via the “zipper” mechanism, the folds are observed to unfold with the lipids re-entering the monolayer before the peptide aggregates. Our results show several key trends. The addition of POPG to the DPPC monolayer has a fluidizing effect, which assists monolayer folding. In contrast, the addition of PA has a condensing effect. The addition of peptides fluidizes the monolayer and accelerates the folding processes. If the peptides are allowed to aggregate, the peptide aggregate nucleates a defect in the monolayer, further assisting the folding process. The results also show a clear system-size dependence that affects the folding mechanism observed. If the system size is large enough peptide containing monolayers can fold without the formation of a peptide aggregate.

Membrane Structure II

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Structural Changes in DMPG upon changes of ionic strength and pH - What to learn from SANS, DSC, FCS, Fluorescence Microscopy, FTIR and Viscosity Measurements

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Commonly pure phospholipid membranes are used as models for the more complex real biological membranes. Self-assembling the phospholipids can exhibit a number of different lamellar and nonlamellar phases. They are undergoing a cooperative melting reaction, which is linked to loss in conformational order of the lipid alkyl chains. In certain cases, like for aqueous dispersions of dimyristoyl phosphatidylglycerol (DMPG) a negatively charged phospholipid, this is resulting in an extended network system. The transitions associated are depending on temperature, pressure, lipid concentration and sample environment, such as ionic strength and the pH value (Schneider, M. F. et al., PNAS, 96 (1999) 14312; M.T. Lamy-Freund, K.A. Riske, Chem. Phys. Lipids, 122 (2003) 19).

We studied DMPG dispersions under different pH and ionic strength conditions using methods gaining complementary information about the changes in mate-

rial properties. In particular we studied the structural changes using small angle neutron scattering (SANS) as well as fluorescence microscopy and the thermodynamically by differential scanning calorimetry (DSC). In addition rheology, Fluorescence Correlation Spectroscopy (FCS) and Fourier-Transform Infrared Spectroscopy (FTIR) was performed. This results in a comprehensive model, taking into account the thermodynamic and structural changes below, in and above the region of the phase transition.

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Formation of Block Liposomes is a General Phenomenon of Charged Membranes

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We have recently reported on the discovery of block liposomes (BLs), a new class of chain-melted (liquid) vesicles, formed in mixtures of curvature-stabilizing hexadecavalent cationic lipid MVLBG2, DOPC and water (Zidovska et al., *Langmuir*, 2008). BLs consist of distinctly shaped, yet connected spheres, pearls, tubes, or rods. Unlike typical liposome systems, where spherical vesicles, tubular vesicles, and cylindrical micelles are separated on the macroscopic scale, within a BL, shapes are separated on the nanometer scale. We carried out structural studies of BLs with differential-contrast-microscopy (DIC) and cryo-transmission-electron-microscopy (cryo-TEM) and identified membrane charge and spontaneous membrane curvature as key parameters controlling the BL-formation. BL-formation was believed to be a special capacity of MVLBG2, a newly synthesized highly charged (16+) lipid (Ewert et al., *JACS*, 2006) with giant dendrimer-like headgroup leading to a conical molecular shape resulting into high spontaneous membrane curvature, when incorporated into lipid bilayer. In this work we report formation of BLs for other cationic lipids, demonstrating that BL-formation is a general phenomenon of all charged membranes. We carried out systematic study of binary lipid mixtures comprised of DOPC and a cationic lipid, varying the headgroup size and charge of cationic lipid from 1+, 3+ to 5+. We find that all cationic lipids form BLs on the micrometer and nanometer scale. We have also found that pure DOPC forms BLs in presence of monovalent salt, which is known to cause zwitterionic DOPC to become negatively charged. This latter finding confirms that BL-formation is a general capacity of charged membranes independent of the charge nature. Block liposomes may find a range of applications in chemical and nucleic acid delivery and as building blocks in the design of templates for hierarchical structures. Funding by DOE DE-FG-02-06ER46314, NIH GM-59288, NSF DMR-0503347.

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Lipid Bilayer Pre-Transition as the Beginning of the Melting Process: a Periodic Melting

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We investigate the bilayer pre-transition, which some lipids present at temperatures below their main phase transition, and which is generally associated to the formation of periodic ripples. Experimentally, we focus on the ubiquitous dipalmitoylphosphatidylcholine (DPPC) and on its charged analog dipalmitoylphosphatidylglycerol (DPPG) at different ionic strengths. Analysis of the excess heat capacity of DPPC and DPPG shows that both pre- and main transitions are part of the melting process. The cooperativeness of DPPG is lower at low ionic strength. Electron spin resonance of spin labels located at the bilayer center reveals the coexistence of gel and fluid domains at temperatures between the pre- and main transitions. Excitation generalized polarization of Laurdan also suggests microphase coexistence in the ripple phase of both lipids. To broaden the knowledge on the ripple phase, we introduce a new statistical model where a next-nearest-neighbor competing interaction is added to the usual two-state model. For the first time, modulated phases, with ordered and disordered lipids naturally appearing in a periodic fashion, are obtained between the homogeneous gel and fluid phases. A better understanding of the different interactions among lipids in a bilayer is of fundamental importance to the full knowledge of the biophysics of natural membranes.

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Phase Transitions In Charged-lipid Membranes: A Statistical Model

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