Manipulating Metastability in Lipid-based Multi-lamellar Particles

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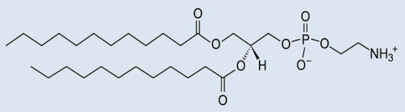
Phospholipids and their Self-Assembly

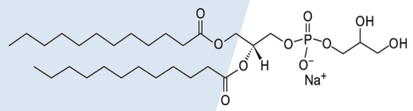
Phospholipids are a main component of cell membranes and can form various structures via the self-assembly process.

We study the phase-transition thermodynamics of DLPE and DLPG phospholipid bilayers in solution. DLPE is known to have a highly ordered crystalline structure at temperatures below 43°C [1,2].

Multi-lamellar Vesicle (MLV)



Dilauroyl-phosphatidylethanolamine (DLPE)
12 carbon saturated chains, zwitterion

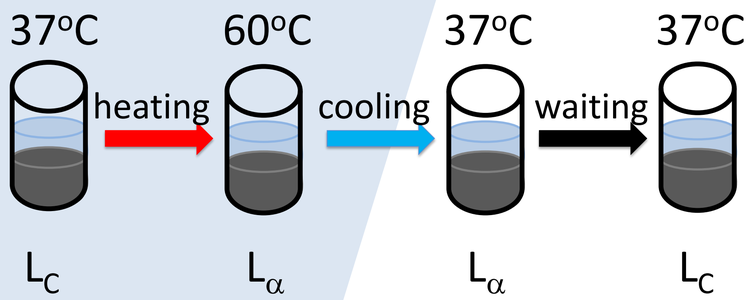


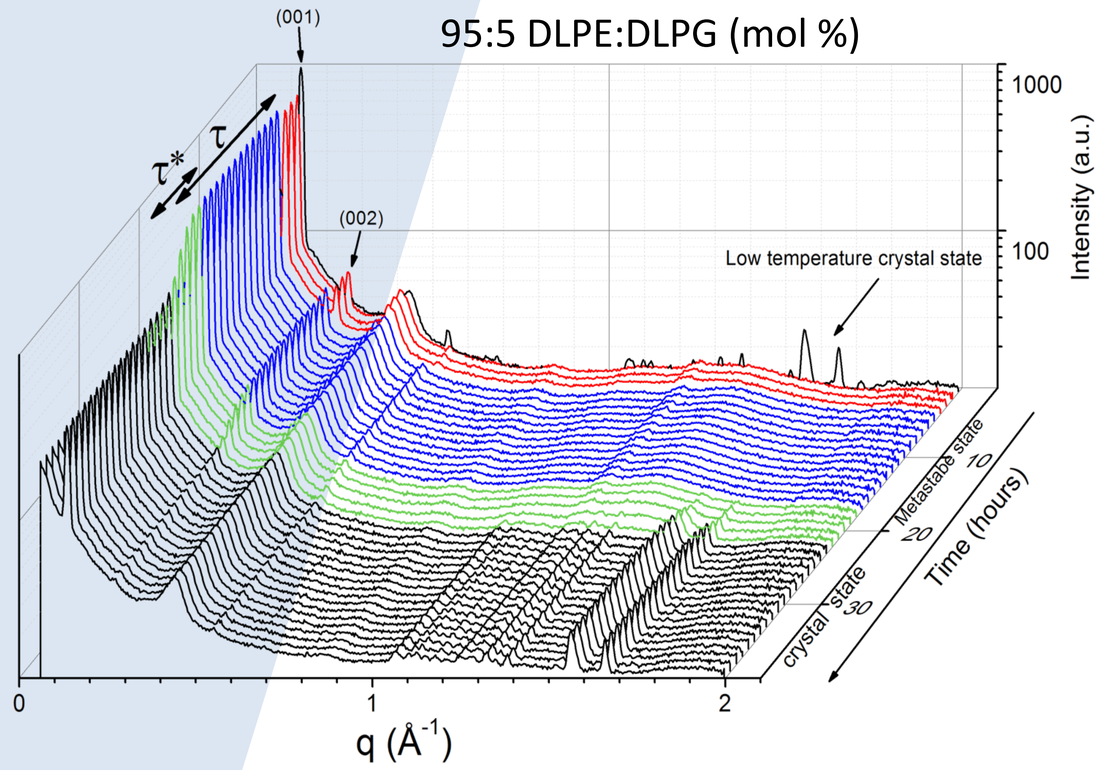
Dilauroyl-phosphatidylglycerol (DLPG)
12 carbon saturated chains, negative charge

[1] Chang, H. & Epand, R. M (1983). *Biochimica et Biophysica Acta,* 728 (1983) 319-324
[2] Seddon, J. M., Harlos, K., & Marsh, D. (1983). *Journal of Biological Chemistry*, *258*(6), 3850–3854

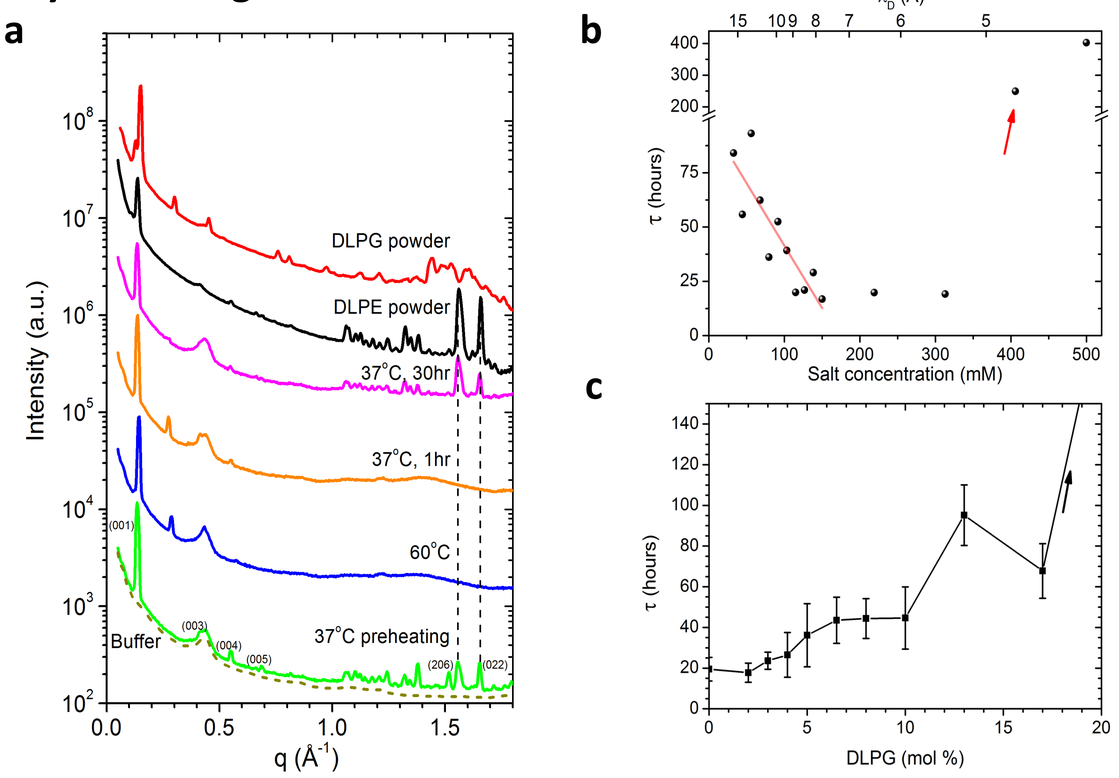
The Metastable Liquid-Crystal phase

Time resolved x-ray scattering experiments on DLPE:DLPG dispersions at full hydration. At 37°C, pure DLPE crystalline phase is present in the sample. After heating to 60°C the hydrocarbon chain correlations disappear (wide angle peaks) corresponding to MLVs in the liquid-crystalline phase (L_α). Upon re-cooling to 37°C the L_α phase becomes metastable for tens of hours (denoted $\boldsymbol{\tau}$ – delay time) until a collective phase transition back to crystalline state on a shorter time scale (denoted $\boldsymbol{\tau}^*$ – transition time).





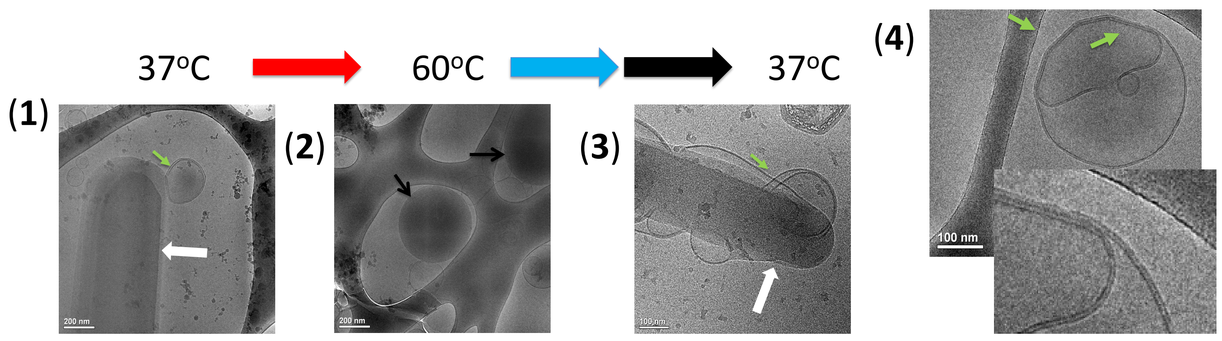
X-ray Scattering



a. X-ray scattering data of DLPE:DLPG 95:5 (mol:mol%) representative of the different stages of the experiment, compared with dry DLPE and DLPG powder scattering. Dashed lines mark the positions of 2 distinctive wide angle x-ray scattering peaks. **b**, With the addition of salt, at low concentrations (<150 mM), the delay time (τ) decreases, while at high concentrations (>300 mM), there is an order of magnitude increase in delay times (τ). **c**, The delay time (τ) strongly depends on DLPE:DLPG (mol%) ratio.

Cryo-TEM

(**1**) A population of large crystals (>1μm) visible prior to heating. (**2**) At 60°C the crystals melt to form MLVs with water situated between the bilayers. Cooling back to 37°C, (**3**) reforming crystals and (**4**) sharp faceted liposomes.



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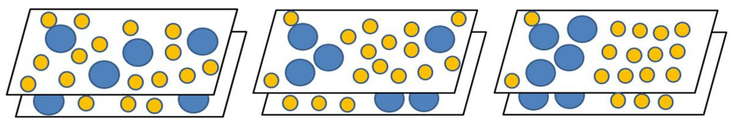
Competing forces for crystallization

DLPE crystallization Neck/channel formation	⟷	Lipid segregation Membrane undulation Membrane elasticity Water & ion permeability 2D crystal's destabilization

37°C → 60°C → 37°C



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