NMRlipids IV: Other than PC headgroups

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Primarily measured but also simulated NMR order parameters will be collected also for other than phophatidylcholine (these are discussed in NMRlipids I) headgroup. The information will be used to understand structural differences between different lipid molecules in bilayers.

INTRODUCTION

Phospholipids containing various polar headgroups and acyl chains are essential building blocks of biological membranes. Atomistic level structural details of lipids and lipid-ion interactions are considered highly important in several biological processes. The lipid structure and ion binding can be studied in detail with NMR spectroscopy. However, the structural interpretation of NMR data requires usage of models. The combination of classical molecular dynamics simulations with NMR data, especially with C-H bond order parameters, can potentially give atomistic resolution interpretation of structure and dynamics of molecules [1–3].

Our recent studies concluded that MD models are cabable to give structural interpretation for phosphatidylcholine hydrophopic acyl chain region, while hydrophilic headgrop, glycerol backbone and cation binding posed a major challenge for current force fields [1–4]. These conclusions were reached by reviewing extensively available experimental data from various sources and using NMRlipids Open Collaboration project to collect massive amount of simulation data [1, 4].

Here we apply the same approach in search of MD simulation models which would reproduce glycerol backbone and headgroup structures of lipids with PE, PG and PS headgroups. In addition, we attempt to find a MD simulation model that would be able to correctly describe cation binding in bilayer containing negatively charged PG and PS lipids.

EXPERIMENTAL GLYCEROL BACKBONE AND HEADGROUP ORDER PARAMETERS FOR PE, PG AND PS LIPIDS

Absolute values of experimental order parameters for different lipid headgroups are collected in Fig. 1. Signs are measured only for PC as far as I know, thus only absolute values are used for now.

Based on superficial reading, the conclusions in the literature are roughly 1) glycerol backbone structures are largely similar irrespectively of the headroup [9], 2) glycerol backbone and headgroup strucures are similar in model membranes and in bacteria [9**?**], 3) headgroup structure is phosphatidylserine more rigid than in other phospholipids, which are quite similar to each others [**?**]. In contrast to PC lipids, extensive discussion on glycerol backbone and headgroup structural details do not exist (as far as I know).

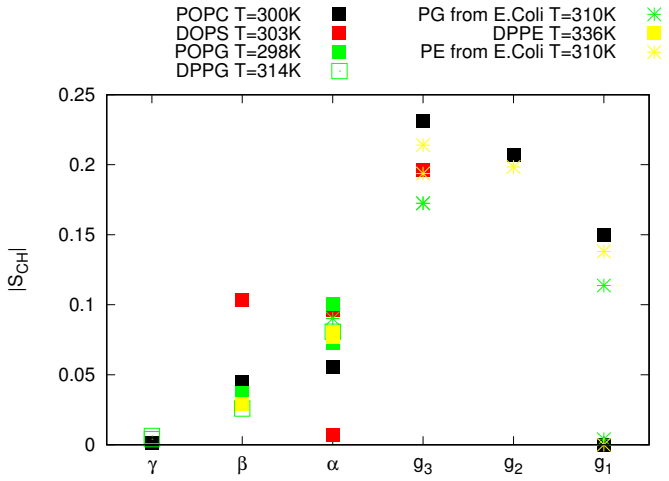

FIG. 1: Absolute values of order parameters for headgroup and glycerol backbone with different headgroups from experiments. POPC values are from [5], DOPS from [6] contains 0.1M of NaCl, POPG from [7] contains 10nM PIPES, DPPG from [**?**] contains 10mM PIPES and 100mM NaCl, DPPE from [8], E.coliPE and E.coliPG are from [9].

GLYCEROL BACKBONE AND HEADGROUP ORDER PARAMETERS FOR PE, PG AND PS LIPIDS IN SIMULATIONS

Several simulations containing PE, PG and PS lipids have been published [**?**], however, glycerol backbone and headgroup order parameters are not compared to the experiments (based on superficial reading of literature).

Glycerol backbone and headgroup order parameters for PS lipids from experiments and simulations are shown in Fig. 2. The preliminary test with CHARMM GUI simulations show suggest that the model overestimates magnitudes in β and g_3 order parameters and forking in α.

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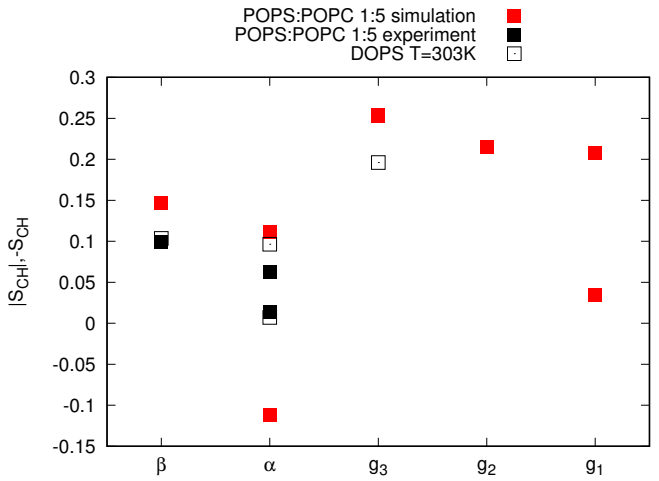

FIG. 2: Order parameters for POPS headgroup and glycerol backbone from simulations and experiments without $CaCl_2$ (DOPS from [6] contains 0.1M of NaCl, POPC:POPS mixture from [11]). Absolute values are shown for experimental data, because signs are not known. Simulations values are -S_{CH}

1.More simulation data for lipids with different headgroups to be collected 2.CHARMM GUI simulation contains only counter ions as potassium. All experiments here contain some amount of sodium salt. The best ion concentrations for comparison should be figured out. 3.Experimental signs of the order parameters would highly useful.

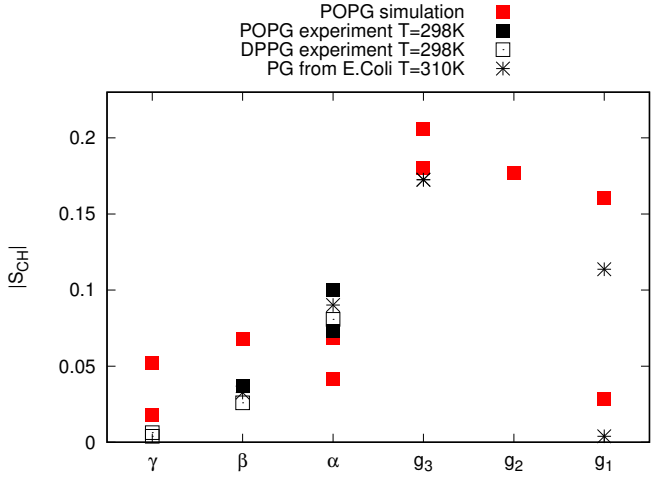

FIG. 3: Order parameters for PG headgroup and glycerol backbone from simulations and experiments without $CaCl_2$ (POPG from [7] contains 10mM of PIPES, DPPG from [**?**] contains 10mM PIPES and 100mM CaCl, E.Coli PG results from [9]). Absolute values are shown, because signs are not known for experimental data. Glycerol backbone order parameters are negative in simulations, while $alpha$, β and smaller γ are positive.

4.More simulation data for lipids with different headgroups to be collected 5.CHARMM GUI simulation contains only counter ions as potassium. All experiments here contain some amount of sodium salt. The best ion concentrations for comparison should be figured out. 6.Experimental signs of the order parameters would highly useful.

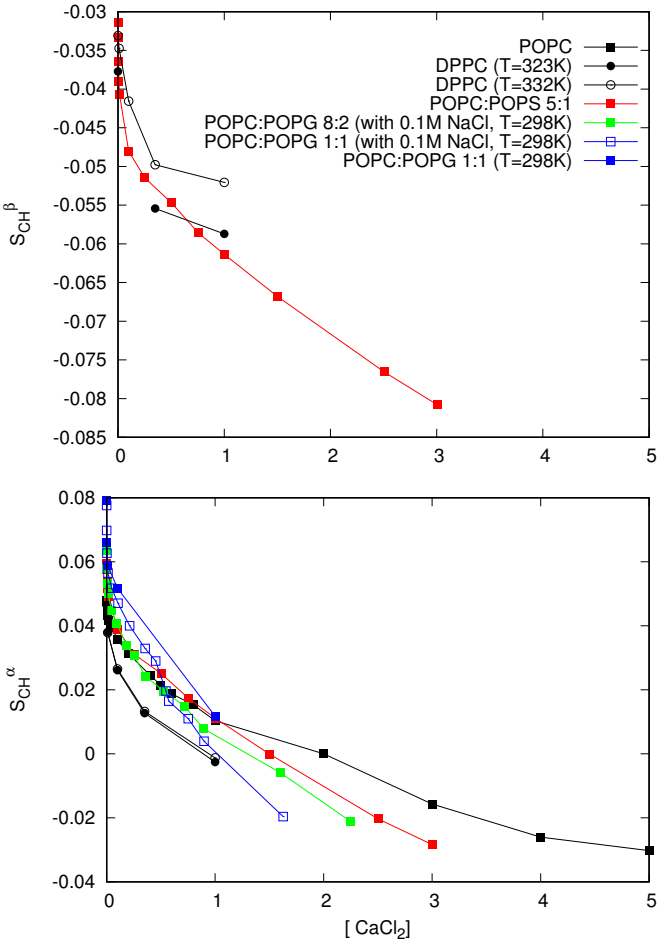

FIG. 4: PC headgroup order parameters as a function of CaCl concentration from experiments containing charged lipids. Pure DPPC data from [12], pure POPC data from [13], POPC:POPS mixture data from [11], POPC:POPG mixture data with 0.1M NaCl from [10] and POPC:POPG mixture data without NaCl from [7].

7.Check the NaCl concentrations in the samples.

CA2+ BINDING IN BILAYERS WITH NEGATIVELY CHARGED PG AND PS LIPIDS

Ion binding affinity in lipid bilayer containing PC lipids can be measured by using C-H bond order parameters for headgroup α and β carbons by using the electrometer concept. The decrease of these order parameters is linearly proportional to the amount of bound charge in bilayer [4**?**]. The electrometer concept can be used also for bilayers containing PC lipids mixed with charged lipids [10**?** , 11]. This is demonstrated in Figs 4, 5 and 6, where PC headgroup order parameters as a function of $CaCl_2$ concentration are shown from experiments with POPC and PS or PG.

Order parameters increase when PS or PG are mixed with PC in the absence of additional ions, as seen from Figs. 4 and 5. In electrometer concept this is explained by the tilting of headgroup more parallel to membrane normal [**?**]. The

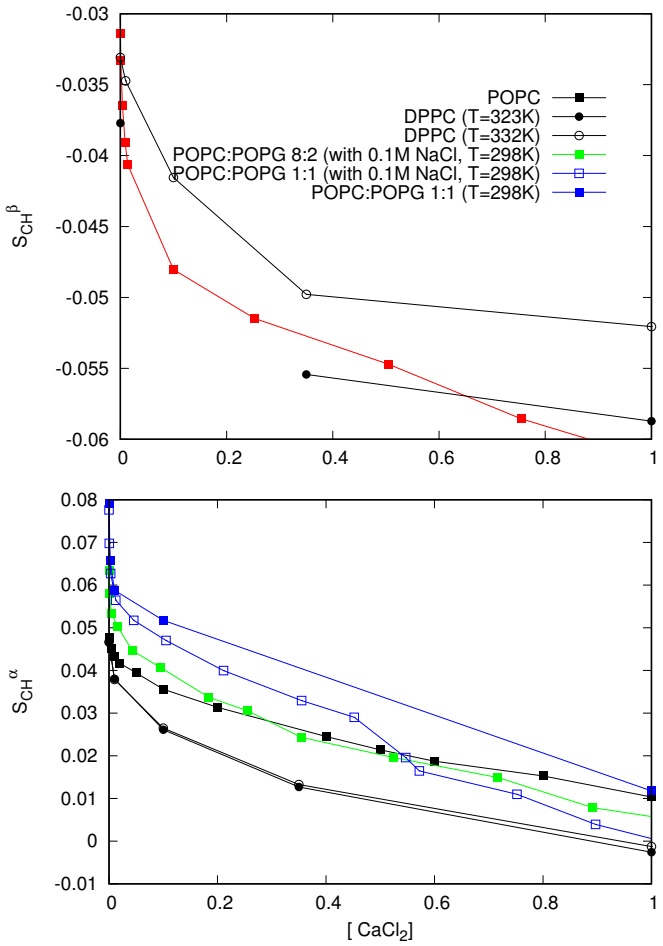

FIG. 5: Figure 4 zoomed to smaller concentrations.

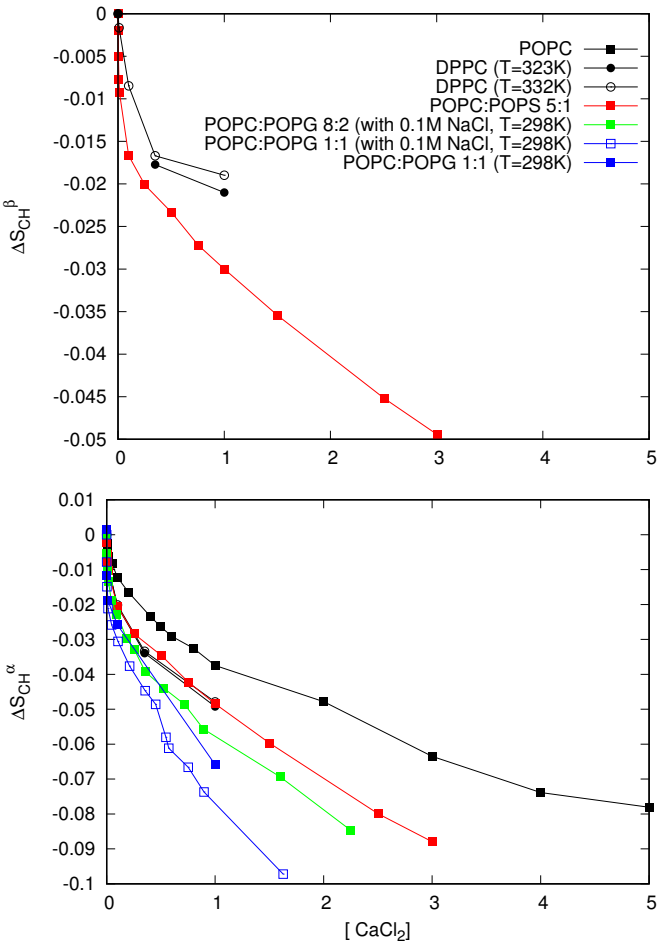

FIG. 6: Changes in order parameters

order parameter decrease with increasing $CaCl_2$ concentration is explained by the tilting of headgroup more perpendicular to membrane normal. This decrease is shown to be a good measure for the amount of bound ions in lipid bilayer with PC lipids [4**?**].

The order parameter decrease as a function of added $CaCl_2$ for systems with different amount of negative charge are shown in Fig. 6. As expected, the order parameter decrease is more pronounced with increasing amount of negatively charged lipids in bilayer. This is explained by the increase of cation concentration in proximity of bilayer containing negatively charged lipids [**?**].

In addition to the changes in PC headgroup order parameters with ion binding, also changes in PS and PG headgroup order parameters are measured.

CA2+ BINDING IN BILAYERS WITH NEGATIVELY CHARGED PG AND PS LIPIDS IN SIMULATIONS

9.Simulation data for systems with negatively charged lipids and $CaCl_2$ to be collected

CONCLUSIONS

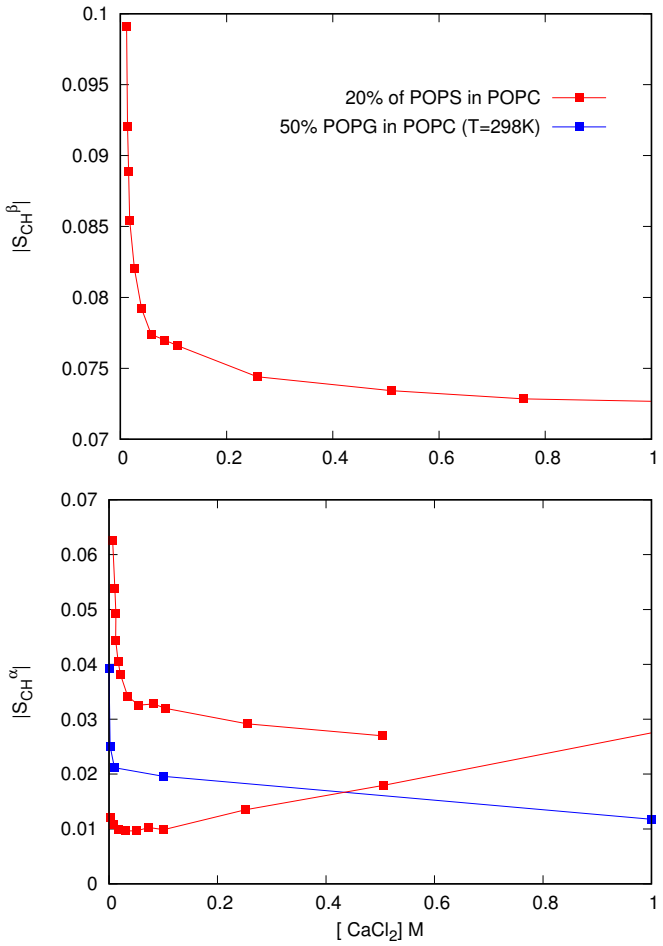

FIG. 7: Changes in order parameters

8.Get the small concentration data from the inserts

SUPPLEMENTARY INFORMATION

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