Towards an Understanding of Cationic Lipid Bilayers from Atomistic Molecular Dynamics Simulations

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Introduction

- Cationic lipids, being a promising class of nonviral vectors for gene delivery, are able to form compact complexes with DNA and to facilitate transfection of DNA into living cells (see e.g. [1])
- Detailed understanding of a structure of the cationic lipid/DNA complexes is needed for the further development of these delivery vectors. However, due to the complex nature of the problem, the only atomistic computer simulation study of such complexes exists [2].
- As a first step toward detailed atomistic study of complexes of cationic lipids and DNA, in this work we employ molecular dynamics (MD) simulations of cationic lipid bilayers in aqueous solution.
- We study a lipid bilayer consisting of a mixture of zwitterionic lipid dimyristoylphosphatidylcholine (DMPC) and cationic lipid dimyristoyltrimethylammonium propane (DMTAP), see Fig. 1.

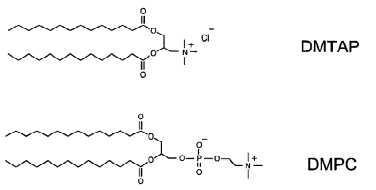


Fig. 1. *Structures of DMPC and DMTAP* [3]*, lipids under study*

- The main **OBJECTIVE** of this study: To understand how the composition of cationic lipid bilayers (i.e. mole fraction of the cationic lipid DMTAP, χ_{TAP}) affects their structural and electrostatic properties.

Model and Simulation Details

- **System:** 128 lipid molecules (64 lipids per monolayer), ∼3600 SPC water molecules, and ions Cl^-. **Total:** ∼17000 atoms.
- United-atom GROMACS force-field modified to describe lipids [4].
- $T = 323\ K$ and $P = 1\ Bar$ (Berendsen coupling scheme).
- Electrostatics: Particle Mesh Ewald (PME)
- 11 different concentrations of cationic lipid DMTAP in bilayer are considered: 0.0 (pure DMPC bilayer), 0.06, 0.16, 0.25, 0.31, 0.39, 0.50, 0.63, 0.75, 0.89, and 1.0 (pure DMTAP bilayer).
- Equilibration: From 10 ns to 20 ns depending on DMTAP concentration χ_{TAP}. Production run: 10 ns.
- Software: GROMACS 3.1.4 [5].

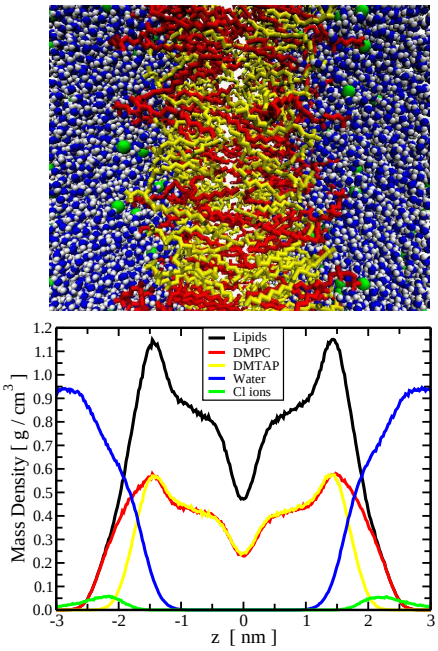


Fig. 2. *(Top) Snapshot of final structure for cationic bilayer at* $\chi_{TAP} = 0.5$ *after 30 ns; (Bottom) Mass density profile across the same bilayer (*$z = 0$ *corresponds to the bilayer center).*

Structural Properties

Area per Lipid, <A>

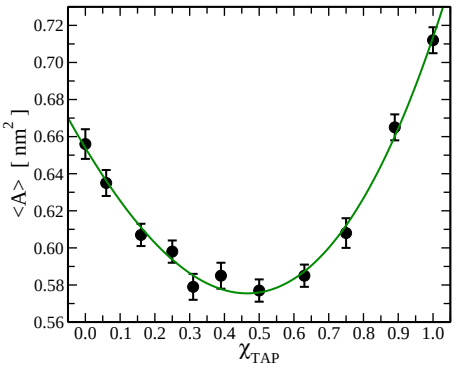


Fig. 3. *Average area per lipid* $\langle A \rangle$ *versus DMTAP fraction* χ_{TAP}.

- **Area per lipid for pure DMPC bilayer at 50°C:**
  Simulation: 0.656 ± 0.008 nm^2
  Experiment: 0.654 nm^2 [6] and 0.629 nm^2 [7].

Orientation of PC Head Groups

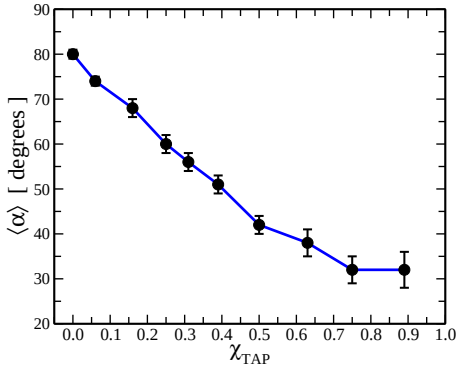


Fig. 4. *Average angle* $\langle \alpha \rangle$ *between the P-N vector of DMPC lipids and the monolayer normal versus DMTAP concentration* χ_{TAP} *in bilayer*

Deuterium Order Parameter

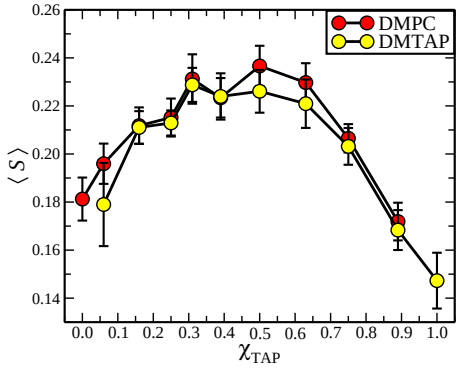


Fig. 5. *Plateau order parameter* $\langle S \rangle$ *calculated by averaging* S_{CD} *over C2 to C8 hydrocarbons.*

Coordination Numbers

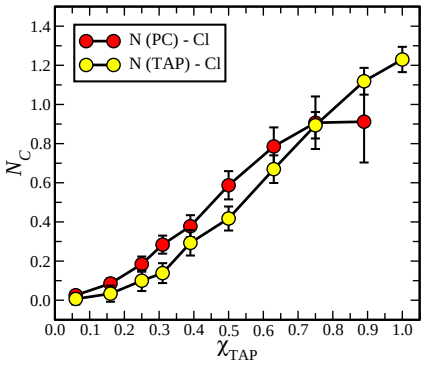
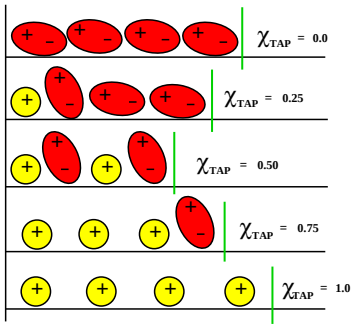


Fig. 6. *Coordination numbers* N_C *of DMPC and DMTAP nitrogens with chloride ions.*

Conclusions

- The average area per lipid has a pronounced **non-monotonic** dependence on the DMTAP concentration χ_{TAP}, with a minimum around the point of equimolar mixture.
- At low and modest DMTAP concentrations, a considerable compression of the bilayer is observed, see Fig. 3. We address this effect to the re-orientation of dipole moments of DMPC head groups with respect to the bilayer normal, Fig. 4.
- In contrast, at higher DMTAP concentrations (when the re-orientations of PC groups is almost finished) there is a substantial expansion of the bilayer that is mostly driven by electrostatic repulsion between positively charged DMTAP head groups.
- Deuterium order parameter $|S_{CD}|$ follows closely the change in the area per lipid: The compression of the bilayer is accompanied by the ordering of acyl chains and *vice versa*.
- Chloride counter-ions are bound mostly to DMPC nitrogens implying stronger screening of PC heads by Cl ions compared to TAP head groups.
- A proposed schematic picture of the observed change in the area per lipid vs DMTAP concentration χ_{TAP}. Only headgroups of DMPC (red ellipses) and DMTAP (yellow circles) lipids are shown; water (not shown) is above the headgroups.



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