

## Polymorphism of Lipid A bilayers in presence of $\text{Al}^{3+}$ at different ionic concentrations of NaCl and $\text{AlCl}_3$

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**Abstract:** Lipid A is the endotoxically active region of the lipopolysaccharide (LPS) molecule composing the outer membrane of Gram-negative bacteria. Lipid A is a highly potent stimulator of the innate and adaptive immune system of mammals. In the last decades, monophosphorilated Lipid A combined with aluminum salts have been commonly used as vaccines adjuvants since it induces similar cytokine profiles as LPS but it is at least 100-fold less toxic [1]. Previous experimental studies have shown a correlation between the chemical structure and aggregation phase of Lipid A and its biological activity [2]. It is also known that different cations can induce transitions from lamellar to non-lamellar arrangement of Lipid A bilayers [3]. Therefore, we have investigated the influence of aluminum cations on Lipid A aggregation phase using atomistic molecular dynamics simulations. We have performed simulations of mono- and diphosphorilated Lipid A bilayers from *E. coli* in presence of  $\text{Al}^{3+}$  at different salt regimes: (a) 0 mM where  $\text{Al}^{3+}$  was added only to neutralize the system total charge. (b) 150 mM NaCl and (c) 150 mM  $\text{AlCl}_3$ . All molecular dynamics simulations were carried out in a *NpT* ensemble, semi-isotropic scheme (1 bar) and temperature of 300K using the GROMACS 4.5.6 program [4]. We have used an extension of GROMOS 53A6 force field for Lipid A [2] and in-house developed tools to analyze curved membrane surfaces [5]. The Lipid A bilayer at 0mM salt concentration kept a lamellar arrangement, with the presence of curvature in the surface of the diphosphorilated Lipid A bilayer. Systems containing  $\text{AlCl}_3$  suffer a structural transition from lamellar to non-lamellar arrangement. Similar behavior was observed for Lipid A bilayers neutralized with  $\text{Al}^{3+}$  and in presence of NaCl. Furthermore, it is observed the full replacement of aluminum by sodium cations on phosphate binding groups of Lipid A. Lipid A bilayers show selective affinity to cations, which influence directly the final aggregation phase of these systems. We are currently investigating the effect of a broader range of concentrations and multisalt solutions on the aggregation and dynamics of Lipid A bilayers.

**Key-words:** Hofmeister effects, Order parameters, Radial distribution function, Cation and membrane hydration

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