

# Effects of imidazolium-based ionic surfactants on the size and dynamics of phosphatidylcholine bilayers with saturated and unsaturated chains



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## ABSTRACT

Imidazolium-based ionic surfactants of different sizes were simulated with 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) bilayers. Regardless of the phospholipid type, larger surfactants at higher concentrations more significantly insert into the bilayer and increase the bilayer-surface size, in agreement with experiments and previous simulations. Insertion of surfactants only slightly decreases the bilayer thickness, as also observed in experiments. Although the surfactant insertion and its effect on the bilayer size and thickness are similar in different types of bilayers, the volume fractions of surfactants in the bilayer are higher for DMPC bilayers than for POPC and DOPC bilayers. In particular, ionic surfactants with four hydrocarbons yield their volume fractions of 4.6% and 8.7%, respectively, in POPC and DMPC bilayers, in quantitative agreement with experimental values of ~5% and ~10%. Also, the inserted surfactants increase the lateral diffusivity of the bilayer, which depends on the bilayer type. These findings indicate that although the surfactant insertion does not depend on the bilayer type, the effects of surfactants on the volume fraction and bilayer dynamics occur more significantly in the DMPC bilayer because of the smaller area per lipid and shorter saturated tails, which helps explain the experimental observations regarding different volume fractions of surfactants in POPC and DMPC bilayers.

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## 1. Introduction

Room-temperature ionic liquids (ILs) are large organic or inorganic salts in the liquid phase at room temperature. Due to their low volatility, non-flammability, high conductivity, and thermal and chemical stability [1–5], they have been widely used for many industrial or environmental applications such as electrolytes and sorption media for catalysis [6,7], battery [8,9], separation process [10,11], synthesis of composite materials [12,13], and hydrolysis of cellulose [14]. However, recent experiments have shown that ILs are toxic to natural organisms in aqueous environments [15–20], indicating that caution is required when ILs are used for those applications. To design ILs that have low toxicity but still retain high efficiency, the mechanism for structural and dynamic effects of ILs on toxicity needs to be understood, which has motivated experi-

mental and simulation studies on the interactions between ILs and membranes.

Dependence of toxicity on the IL size has been experimentally investigated. Evans showed that imidazolium-based ILs with longer hydrocarbon tails more significantly destabilize liposomes and supported lipid bilayers [21–23]. Jeong et al. also showed that longer ILs at higher concentrations more effectively insert into membranes, which induces membrane instability, leading to the lower transition temperature of membranes [24]. Galluzzi et al. found that the surfactant – monolayer interaction can be modulated by the IL-tail length rather than by the electrostatic interactions between headgroups of ILs and lipids [25]. Also, they showed that ILs with short tails insert into the monolayer and reversibly detach from it, while relatively long ILs can only irreversibly insert. Recently, Benedetto et al. performed neutron reflectometry experiments, showing that ILs occupy the volume of ~5% and ~10%, respectively, in palmitoyloleoylglycerophosphocholine (POPC) and dimyristoylglycerophosphocholine (DMPC) bilayers [26], indicating the higher volume fraction of ILs in the membrane composed of saturated

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lipids. However, the effects of membrane components on the IL insertion and bilayer size have not yet been understood, which requires the understanding of the interactions between ILs and membranes at nearly the atomic scale.

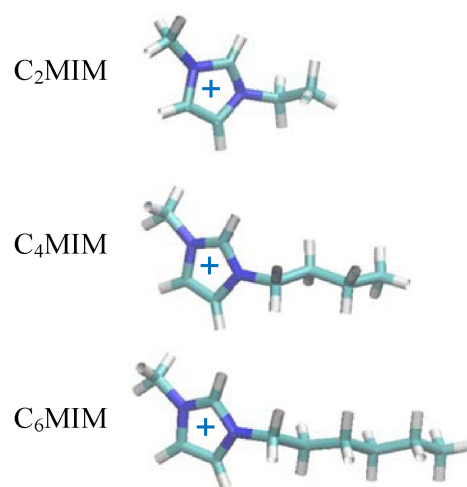
Molecular dynamics (MD) simulations have been performed to understand the interactions between imidazolium-based ionic surfactants and lipid bilayers. Ballone and coworkers simulated ionic surfactants in bilayers consisting of either cholesterol or phospholipids, showing the surfactant adsorption and the preferred position of surfactants and counterions [27,28]. Klahn and Zacharias performed free energy calculations, showing that cholesterol influences the structure and electrostatics of membranes and thus inhibit the insertion of surfactants into the bilayer [29]. Our group simulated self-assemblies of ionic surfactants of different lengths in lipid bilayers, showing the reversible interaction of short surfactants [30], in agreement with Galluzzi et al.'s experiments [25]. In particular, we found that the binding and insertion of surfactants into the bilayer can be modulated by both electrostatic and hydrophobic interactions between surfactants and bilayers, which depends on the tail length of surfactants. Recently, Benedetto et al. found that ILs with chloride ( $\text{Cl}^-$ ) ions increase the diffusivity of POPC bilayers, while those with hexafluorophosphate ( $\text{PF}_6^-$ ) ions decrease the bilayer diffusivity, showing the dependence on anions [31]. Although these simulations support the experimental observations regarding the effects of the ionic-surfactant size, charge, and cholesterol, the dependence on phospholipid types has not been computationally studied.

In this work, we therefore perform MD simulations of differently sized imidazolium-based ionic surfactants in three different phospholipid bilayers with either saturated or unsaturated hydrocarbon tails. The extent of the insertion of surfactants into bilayers and their effects on the bilayer size are analyzed, which are compared to those measured from experiments. Also, the effect of the surfactant insertion on the lateral dynamics of bilayers is investigated, which depends on the phospholipid type. These findings can explain the experimental observations that showed that ionic surfactants occupy the higher volume fraction in the saturated-phospholipid bilayer than in the unsaturated-phospholipid bilayer [26].

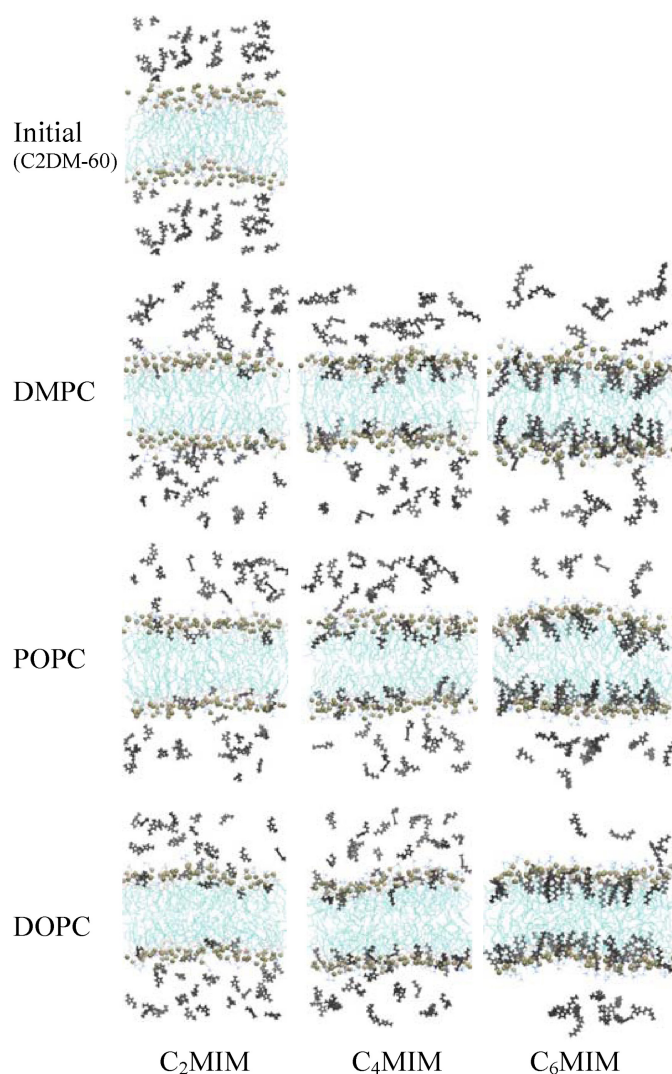
## 2. Methods

All simulations and analyses were performed with the GRO-MACS4.5.5 simulation package [32–34] with the OPLS all-atom force field (FF) and TIP4P water model [35,36]. Imidazolium-based ionic surfactants such as 1-ethyl-3-methylimidazolium ( $\text{C}_2\text{MIM}$ ), 1-butyl-3-methylimidazolium ( $\text{C}_4\text{MIM}$ ), and 1-hexyl-3-methylimidazolium ( $\text{C}_6\text{MIM}$ ) were modeled using the OPLS ionic-liquid FF developed by Sambasivarao and Acevedo [37] (Fig. 1), which has accurately predicted the experimentally observed or theoretically derived structural and thermodynamic properties of ionic surfactants and their solvent effects on the polymer conformation [38], and thus has been widely used for many previous simulations [39–42]. For lipids, potential parameters for dimyristoylglycerophosphocholine (DMPC), palmitoyloleoylglycerophosphocholine (POPC), and dioleoylglycerophosphocholine (DOPC) were taken directly from the Berger lipid FF modified by Tieleman et al. [43,44]. We equilibrated pure bilayers without ionic surfactants, showing the area per lipid of  $62.3 \pm 1.5$ ,  $64.6 \pm 0.2$ , and  $67.7 \pm 0.2 \text{ \AA}^2$ , respectively, for DMPC, POPC, and DOPC bilayers. These are close to experimental values of  $59.9$  (DMPC),  $64.3$  (POPC), and  $67.4 \text{ \AA}^2$  (DOPC) at  $303 \text{ K}$  [45,46].

16 or 60 ionic surfactants were randomly added to the water region of the equilibrated bilayer system (Fig. 2). The final simulated system consists of 16 or 60 ionic surfactants, 128 lipids (64 lipids



**Fig. 1.** Structures of ionic surfactants ( $\text{C}_2\text{MIM}$ ,  $\text{C}_4\text{MIM}$ , and  $\text{C}_6\text{MIM}$ ). Light-blue, blue, and white colors represent C, N, and H atoms, respectively. The images were created with Visual Molecular Dynamics [54].



**Fig. 2.** Snapshots at the beginning (0 ns) and end (400 ns) of simulations with 60 ionic surfactants (0.38 M). Initial configuration is shown only for C2DM-60, but this random configuration is applied for all other systems. Black, brown, and light-blue colors represent ionic surfactants, lipid phosphates and hydrocarbon tails, respectively. For clarity, water and counterions are omitted. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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