



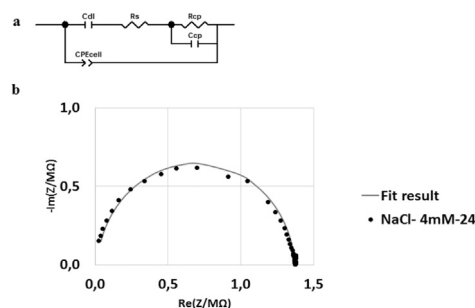
Regular Article

Interaction of anions with lipid cubic phase membranes, an electrochemical impedance study

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GRAPHICAL ABSTRACT



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ABSTRACT

Hypothesis: Electrochemical impedance spectroscopy is useful to monitor anionic interactions with a Lipid Cubic Phase, as previously demonstrated for cationic interaction (Khani Meynaq et al., 2016). It was expected that the smaller hydrophilic anions, acetate and chloride, would interact differently than the large tryptophan anion with its hydrophobic tail.

Experiment: The impedance measurements enabled estimation of resistances and capacitances of a free-standing lipid cubic phase membrane at exposure to 4 and 40 mM solutions of NaCl, NaOAc and NaTrp. Small-angle X-ray scattering was used for cubic phase identification and to track structural changes within the cubic phase when exposed to the different electrolytes.

Findings: The membrane resistance increases at exposure to the electrolytes in the order $\text{Cl}^- < \text{OAc}^- < \text{Trp}^-$. The membrane resistance decreases with time at exposure to the hydrophilic anions and increases with time at Trp^- exposure. The membrane capacitances were lower for NaTrp compared to NaCl and NaOAc at the corresponding concentrations which is consistent with the results from SAXRD. It is concluded that Trp^- ions do not enter the aqueous channels of the cubic phase but are strongly adsorbed to the membrane/electrolyte interface leading to large alteration of the lipid phase structure and a high membrane resistance.

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Abbreviations: EIS, electrochemical impedance spectroscopy; MO, Monoolein; Trp, L-tryptophan; LCP, lipid cubic phase; SAXRD, small angle X-ray diffraction; PC, phosphatidylcholine; MD, molecular dynamics; CPE, constant phase element; NMR, nuclear magnetic resonance; IR, infrared spectroscopy.

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1. Introduction

Lipid cubic phases (LCP) with curved lipid bilayers form fundamental structural units that can be used as model systems for biological membranes [2,3]. An LCP is formed when lipids are mixed with water or aqueous solutions at specified proportions and tem-

perature. So, continuous nanochannels, filled with water, are formed and the structure is defined by curved lipid bilayers.

Monoolein (MO) is a common lipid used for formation of LCP. The MO cubic phase is isotropic, thermodynamically stable and highly viscous. Monoolein has a polar head group with two hydroxyl groups that can form hydrogen bonds with water and a hydrophobic tail with C18-hydrocarbon chain, See Fig. 1a. The thickness of the curved bilayer is around 3.5 nm, and the diameter of the aqueous channel is 5 nm [4,5]. Monoolein is often used for development of cubosomes for drug delivery systems [5–8], protein crystallization [9–11], and biosensing [12–14]. The properties of the MO cubic phase depend on the amphiphilic nature of the lipid itself that provides a large hydrophilic surface area within the water channels that is able to efficiently bind ions and drugs. It has been termed as magic lipid by Kulkarni et al. [15].

During the past three decades the toxic interactions of various hydrocarbons with membranes have received much attention. Hydrophilic molecules and ions tend to stay in the aqueous environment, while large hydrophobic molecules and ions prefer the hydrophobic domain of a biological membrane. The interaction of different ions with LCP could shed more light on observed ionic interactions with the cellular membrane, showing increased toxicities for hydrophobic molecules and ions toward biological systems [16–18]. Bingham et al. studied the interactions of 1-*n*-alkyl-3-methylimidazolium-based ionic liquids with a phosphatidylcholine lipid bilayer [19]. They observed that Cl⁻ remains in solution whereas the larger and less hydrophilic anion hexafluorophosphate forms a thin film on the lipid surface. The highly hydrophobic anion bis(trifluoromethanesulfonyl)imide, precipitates out of the solution, forming ionic droplets deposited on the lipid surface.

Interactions between the lipid and a guest molecule and their effect on cubic phase are important in drug delivery studies with cubosomes. Caffrey et al. investigated the affinity of drugs to hydrophobic and aqueous environments in the cubic phase, the mechanism of mass transport in the LCP and the nature of the interaction between drug and the bilayer/aqueous interface of the LCP [5]. Nazaruk et al. observed the pH-dependent drug release from the cubic phase after loading doxorubicin into the LCP and studying drug interactions with the lipidic matrix [20]. They suggested that partitioning of the drug molecule between the LCP hydrophilic/hydrophobic domains depends on pH: doxorubicin is uncharged at high pH and protonated at low pH. The uncharged drug is incorporated into the hydrophobic domain whereas the protonated drug tends to the hydrophilic domain. This means that the drug is released at low pH.

L-tryptophan (Trp) is an α -amino acid with pKa values of 2.38 (carboxyl) and 9.39 (amino) having the chemical structure shown in Fig. 1b. The role of Trp in brain serotonin synthesis is well-known and is a factor that affects mood, behavior and cognition [21,22].

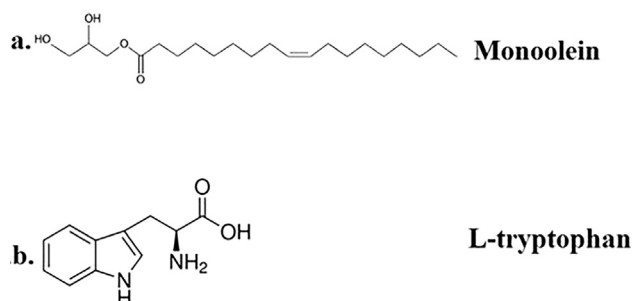


Fig. 1. The molecular structure of (a) Monoolein and (b) tryptophan in neutral form.

The mechanism of interaction of molecular anions and cations with phospholipid membranes in aqueous salt solutions was investigated by molecular dynamics simulations [23,24], colorimetric assay and scanning electron microscope (SEM) [25], nuclear magnetic resonance (NMR) [26], fluorescence solvent relaxation [27], equilibrium-dialysis and spectrophotometry [28], equilibrium dialysis and spin label techniques [29]. Vácha et al. reported that halide anions do not show a strong interaction with the lipid head-groups but compensate the positive charge of the counter-cations [23]. Sagar et al. reported that cation interaction is close to the bilayer surface whereas chloride ions do not penetrate into the headgroup region [30].

The purpose of this paper is to extend our previous work with EIS investigations of cationic interaction in the water channels of a cubic phase [1] to anionic interactions. A freestanding LCP membrane was exposed to NaCl, NaOAc and NaTrp electrolyte solutions. Brown et al. used a similar setup for investigation of a freestanding phytantriol Q²²⁴ cubic phase [31]. Their investigation focused on the effect of temperature, ionic strength, and the potential applied across the membrane, on the membrane resistance. In their case the cubic phase was in equilibrium with the surrounding electrolyte before starting impedance measurements. Interestingly they found a switching between high and low resistance when changing the temperature and when high bias voltages were applied. An increasing membrane resistance with decreasing ionic strength was also observed.

In the present paper we use changes in membrane capacitance and resistance together with small angle x-ray diffraction (SAXRD) to explore the effect of different electrolytes on the mesophase structure and also the interaction with the phospholipids in the channels of the cubic phase.

2. Experimental

2.1. Materials

Monoolein (1-oleoly-*rac*-glycerol) was purchased at >99% purity, Sigma) and used without further purification. L-tryptophan (MW 204.2 g/mol), sodium chloride and sodium acetate were obtained from Sigma-Aldrich. Milli Q water was used for all sample preparations. Milli-Q water system provides very good water quality in terms of ionic purity (18.2 M Ω -cm) at 25 °C consisting of a carbon filter cartridge, two ion exchange filter cartridges, and an organic removal cartridge.

2.2. Instrumentation

Electrochemical impedance spectroscopy measurements were carried out with a ModuLab ECS instrument (Solartron Analytical) at an amplitude of 10 mV and in the frequency range: 0.1 Hz–100 kHz. A two-electrode setup was employed for impedance measurement with two identical Pt electrodes at open circuit potential and with a bias of Zero Volt. All electrochemical measurements were performed at room temperature. EIS data were fitted to circuit models with the ZView software (version 3.4). SAXRD experiments were performed on the Bruker NanoStar diffractometer (Cu K α radiation, cross-coupled Goebel mirrors, three-pinhole collimation system, Vantec 2000 area detector) at the University of Warsaw, Poland. Data was analyzed using Bruker Topas 3 software, by fitting to the so-called 'hkl phase'.

2.3. Lipid cubic phase preparation

Samples were prepared by weighing appropriate amounts of MO and distilled water in a glass vial (38%water and 62% MO)

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