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Effect of methanol on the phase-transition properties of glycerol-monopalmitate lipid bilayers investigated using molecular dynamics simulations: In quest of the biphasic effect

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ABSTRACT

The effect of methanol on the phase and phase-transition properties of a $2 \times 8 \times 8$ glycerol-1-monopalmitate bilayer patch is investigated using a series of 239 molecular dynamics simulations on the 180 ns timescale, considering methanol concentrations c_M and temperatures T in the ranges 0–12.3 M and 302–338 K, respectively. The results in the form of hysteresis-corrected transition temperatures T_m are compatible with the expected features of the biphasic effect, with a reversal concentration c_{rev} of about 5.2 M. Below this concentration, the main transition is between the liquid crystal (LC) and gel (GL) phases, and T_m decreases upon increasing c_M. Above this concentration, the interdigitated (ID) phase is the stable ordered phase instead, and T_m slightly increases upon increasing T up to about 10 M. The analysis of the structural and dynamical properties also reveals very different sensitivities and responses of the three phases to changes in c_M. In particular, the properties of the GL phase are insensitive to c_M, whereas those of the LC and ID phases are altered *via* an increase of the area per lipid. For the LC phase, increasing c_M promotes disorder and fluidity. For the ID phase, in contrast, increasing c_M up to about 10 M slightly increases the ordering and rigidity. Two side issues are also addressed, concerning: (i) the occurrence tilt-precession motions in the GL and ID phases; (ii) the influence of the pressure coupling scheme employed in the simulations, semi- or fully-anisotropic, on the simulation results.

1. Introduction

Lipid bilayers, the main component of biological membranes, are of crucial importance for all living organisms because they form a barrier separating different cellular compartments, define the boundary of the cell, and represent its first interaction site with the extracellular medium [1]. Aqueous lipids can present many different phases [2,3] depending on the types of the lipid molecules, the extent of hydration and the composition of the aqueous phase, as well as on pressure and temperature. The two biologically most relevant of these phases are bilayer phases, namely the gel (GL) and the liquid crystal (LC) phases (Fig. 1, two bottom left panels). They can be distinguished by the arrangement of the lipids within the bilayer as well as by differences in the area per lipid, in the bilayer thickness and in other properties. In the GL phase, the aliphatic lipid tails are arranged in nearly all-*trans* conformations and in orientations that are generally tilted with respect to the bilayer normal [2]. In the LC phase, the aliphatic tails are conformationally disordered (mixture of *trans* and *gauche* conformations) and no preferential collective orientation of the chains (tilting) is observed. For a given bilayer composition and given specified environmental conditions, the temperature at which the GL ↔ LC transition occurs is called the main transition (or melting) temperature T_m. Characterizing the transition temperature of lipid bilayers and the influence of composition and environment on this temperature is of fundamental biological and technological importance [2,4].

There are three basic mechanisms by which the mechanical and permeability properties of the cell membrane can be modulated by cosolutes present in the intra- or extra-cellular medium: (i) direct interaction of the cosolute molecules with specific membrane-bound proteins such as ion or water channels [5–8]; (ii) direct alteration of the phase properties (structure, fluidity, melting temperature) of the bilayer induced by lipid–cosolute interactions [9–12]; (iii) indirect modulation of the properties of membrane-bound proteins *via* an alteration of the bilayer phase properties [13–16]. While the first type of mechanism implies the existence

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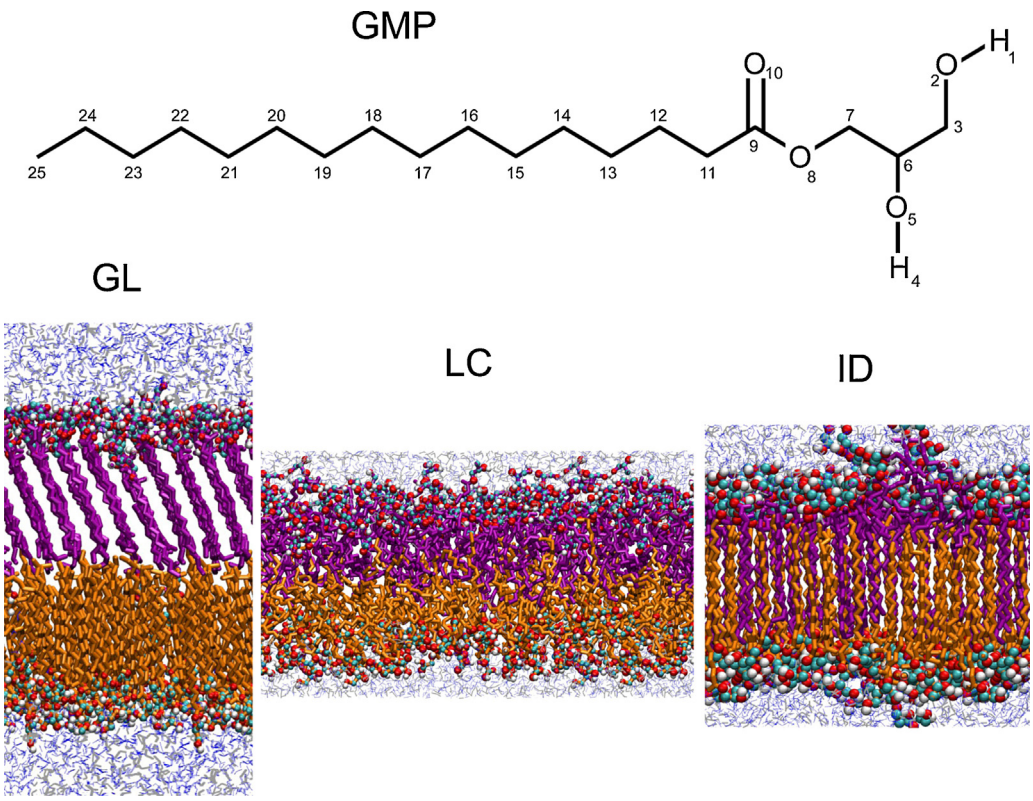

Fig. 1. Chemical structure and bilayer phases of the monoglyceride considered in the present study. The top panel shows the lipid considered, glycerol-1-monopalmitate (GMP), the numbering referring to the GROMOS molecular topology used in the simulations. See Ref. [81] and Suppl. Mat. therein for detailed force-field information. The three bottom panels show illustrative structures for the three phases, gel (GL), liquid crystal (LC) and interdigitated (ID), occurring in the simulations (trajectory frames at 60, 240 and 600 ns, respectively in simulation $M_E F_{GL}310$ of Ref. [81]). The lipids are colored in orange and purple to distinguish the two leaflets (bottom and top, respectively), MET molecules are displayed in grey and water molecules in blue. The atoms of the headgroup are colored according to the element (C1, C2, C3: light blue, O1, O2, O3: red, and H1, H2: white). Note that the structure for LC is shown along the *x*-axis of the box, while the structures for GL and ID were rotated around the *z*-axis to highlight the structural characteristics (alignment or interdigitation). The simulation labels and conditions are summarized in Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

of a specific protein receptor for the cosolute, the two others rely on a generic form of lipid–cosolute interactions. Important mechanisms of the second and third types are responsible, respectively, for the phenomena of anhydrobiosis in the presence of, *e.g.* sugars [9,17–20] and of anesthesia in the presence of, *e.g.* xenon [12], alcohols [11,21] or other small molecules [21].

The phenomenon of anesthesia [15,16,22] corresponds to a reversible loss of consciousness caused by an anesthetic drug. Other attributes such as immobility, analgesia, amnesia and muscle relaxation are closely connected to this phenomenon [15,23]. The exact mechanism of anesthesia is still matter of debate [15,21,24,25]. Depending on the type of anesthetic, it may involve either an interaction with specific receptors [15,16,22,23,26], a direct alteration of the membrane properties [22,25,27], or an indirect influence on membrane-bound proteins [28]. In the apparent absence of specific protein receptors for aliphatic alcohol molecules [3,16], it seems that the mechanism of anesthesia relies in this case on an indirect modulation of the properties of membrane-bound proteins *via* an alteration of the bilayer phase properties [25].

The interaction of alcohols with membranes is further complicated by the biphasic effect [29]. Depending on the concentration range, short-chained aliphatic alcohols have an opposite influence on T_m. At low concentrations, T_m decreases with increasing alcohol concentration, whereas at high concentrations, the opposite trend is observed. The biphasic reversal concentration c_{rev} at which this inversion takes place strongly depends on the nature of the alcohol [30] and on the length of the lipid acyl chains [29]. The biphasic effect is explained by the alcohol-induced formation of an interdigitated (ID) phase (Fig. 1, bottom right panel), where lipid molecules from the two leaflets of the bilayer interpenetrate [31–34]. At low alcohol concentrations, the GL phase is increasingly destabilized relative to the LC phase, due to the intercalation of alcohol molecules between the lipid headgroups and the resulting increase in the area per lipid, leading to the observed T_m decrease. At high concentrations, the ID phase can be formed, its stability relative to the LC phase increasing with the alcohol concentration, leading to the observed T_m increase. Note that this description relies on a slightly "informal" definition of T_m, which characterizes in the usual way a GL ↔ LC transition below c_{rev}, but an alternative ID ↔ LC transition above c_{rev}.

The occurrence of an ID phase at high alcohol concentrations can be interpreted as an extreme consequence of the same effect that induces the T_m decrease at lower concentrations, namely the intercalation of the alcohol molecules between the lipid headgroups [32–36]. This results in an increase of the effective headgroup volume, inducing a lateral expansion in the interfacial region [37–39]. When this expansion is sufficiently pronounced, the void spaces within the bilayer interior can be removed through interdigitation of the lipid tails [31–34,36–41]. All short-chain aliphatic alcohols, from methanol (MET) through heptanol, induce interdigitation at sufficiently high concentrations [30,37,40,41]. However, longer chain alcohols may lead to a different response, presumably because their aliphatic chains are also able to intercalate between the lipid tails [42–44].

Atomistic molecular dynamics (MD) simulations have greatly contributed to the characterization and understanding of the structure, thermodynamics and dynamics of lipid bilayers under various conditions [10,45,21,51,46–50,11,52–62]. These