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Geometrical effects of phospholipid olefinic bonds on the structure and dynamics of membranes: A molecular dynamics study

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ABSTRACT

The *trans* isomers of fatty acids are found in human adipose tissue. These isomers have been linked with deleterious health effects (*e.g.*, coronary artery disease). In this study, we performed molecular dynamics simulations to investigate the structures and dynamic properties of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphatidylcholine (POPC) and 1-palmitoyl-2-elaidoyl *sn*-glycero-3-phosphatidylcholine (PEPC) lipid bilayers. The geometry of the olefinic bond and membrane packing effects significantly influenced the conformations and dynamics of the two C – C single bonds adjacent to the olefinic bond. For the PEPC lipid, the two C – C single bonds adjacent to the olefinic bond adopted mainly nonplanar *skew–trans* and planar *cis–trans* motifs; although the *cis* conformation featured relatively strong steric repulsion, it was stabilized through membrane packing because its planar structure is more suitable for membrane packing. Moreover, membrane packing effects stabilized the planar transition state for conformational conversion to a greater extent than they did with the nonplanar transition state, thereby affecting the dynamics of conformational conversion. The rotational motions of the first neighboring C – C single bonds were much faster than those of typical saturated C – C single bonds; in contrast, the rotational motions of the second neighboring C – C single bonds were significantly slower than those of typical saturated torsion angles. The packing of PEPC lipids is superior to that of POPC lipids, leading to a smaller area per lipid, a higher order parameter and a smaller diffusion coefficient. The distinct properties of POPC and PEPC lipids result in PEPC lipids forming microdomains within a POPC matrix.

1. Introduction

Phospholipids are the main components of cell membranes. Their structures and compositions regulate various properties of the membrane, including fluidity and permeability. Phosphatidylcholines (PCs) are the most abundant phospholipids in animal cell membranes; among them, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphatidylcholine (POPC) is probably the most common naturally occurring PC [1]. POPC [Fig. 1(a)] features two asymmetric acyl chains: a fully saturated *sn-1* chain and a monounsaturated *sn-2* chain with a *cis* olefinic bond. A *cis* conformation for the olefinic bond is required in lipids for their biosynthesis; it provides the stereoselective and regiospecific enzymatic activity of the desaturases [2]. The *trans* isomers of naturally occurring *cis*-unsaturated fatty acids and phospholipids have traditionally received less attention than their counterparts. With the development of advanced analytical methods, however, more new *trans*-unsaturated lipids have been identified [3], mostly in the membranes of prokaryotes and algal chloroplasts [4]. The enzymatic *trans*-to-*cis* conformational conversion of unsaturated lipids in the membranes of some bacteria is thought to be a short-term strategy for adaption under different physiologically stressful conditions. In the membranes of Gram-negative bacteria, the *trans*-to-*cis* ratio of unsaturated lipids increases in response to increased temperature [5], starvation and desiccation [6], hypo-osmotic shock [7], and the presence of organic solvents [8]. In membranes, modification in the *trans*-to-*cis* ratio of unsaturated lipids changes the membrane fluidity.

The *trans* isomers of fatty acid found in human adipose tissue are assumed to derive from dietary intake. These isomers are present in foods containing fats and oils, particularly those processed through partial hydrogenation, deodorization, or frying at high temperatures [9]. The *trans* isomers of fatty acids have also been linked to deleterious health effects (*e.g.*, coronary artery disease) and risk factors for heart attacks. The *trans* fatty acids can be incorporated into phospholipids constituting the cell membrane. Similar to the naturally occurring lipid isomers, *trans*-lipids can enter the cell metabolism process and give rise to various compounds that influence cell properties and functions [10,11].

Experimental [12,13] and molecular dynamics [14–16] studies of model membranes have revealed that the site of monounsaturation and the conformation (*cis* or *trans*) of the olefinic bond affect the order and packing of the hydrocarbon chains. The presence of *cis* olefinic bonds in lipids increases the water penetration of the model membrane

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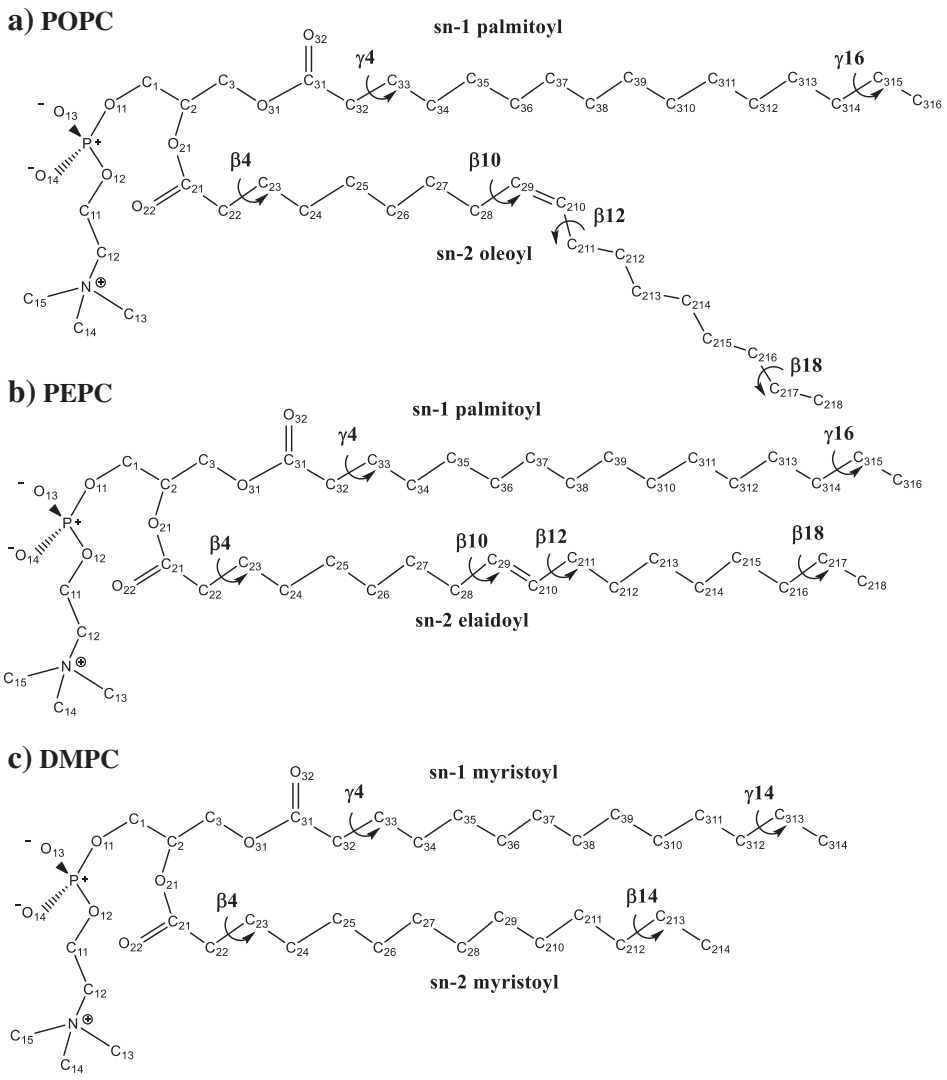

Fig. 1. The chemical structure and labeling of (a). POPC lipid, (b). PEPC lipid, and (c). DMPC lipids.

relative to that of *trans* olefinic bonds [11,17]. Moreover, the water permeability is mainly determined by the area per lipid [18]. Fluorescence measurements [17] have revealed that the fluidity of *cis* lipids is higher than that of *trans* lipids. In a mixed system of *cis* and *trans* lipids, the *trans* lipids formed ordered and thermostable domains [19].

The presence of an olefinic bond in an alkyl chain will affect the chain's conformation—in particular, the conformation of the torsion angle next to the olefinic bond. Fundamental studies of 1-butene using *ab initio* calculations [20] and microwave spectroscopy [21] have revealed that the torsion angle next to the olefinic bond adopts a *skew* or *cis* conformation. Thus, the torsion angles of single bonds next to olefinic bonds are unlikely to form the *trans* or *gauche* conformations that are usually observed in saturated alkyl chains. For mono-*cis*-unsaturated chains, X-ray diffraction experiments have indicated that the torsion angles next to the olefinic bonds prefer to populate *skew* (120°) and *skew*′ (−120°) conformations [22,23]. For better understanding, the *skew* and *skew*′ conformations of the first C–C single bond neighboring an olefinic bond present in Newman projection were displayed in the Fig. S1. Earlier short-time molecular dynamics (MD) simulations (15 ns) of POPC lipid bilayers using united-atom OPLS parameters have revealed that the torsion angles next to the *cis* olefinic bonds are broadly distributed from *gauche* (60°) to *gauche*′ (−60°) with a maximum at *trans* (180°) conformation [16]. Recent MD simulations of POPC lipid bilayers using the OPLS-AA force field [24], and of 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC) lipid bilayers [25] using a force field with olefinic bond description by Bachar et al. [26], have revealed that the torsion angles next to the *cis* olefinic bond are mainly populated at *skew* conformations; these simulation results are in good agreement with experimental observations of, for example, area per lipid and order parameters.

When considering steric effects, we might expect that the torsion angles of the single bonds next to *trans* olefinic bonds in monounsaturated lipids or fatty acids would be different from those next to *cis* olefinic bonds. The crystal structure of mono-*trans*-unsaturated elaidic acid has revealed that the torsion angles next to the *trans* olefinic bond adopt *skew* and *skew*′ conformations [27,28]. Using the united-atom force field OPLS, MD simulation [16] of 1-palmitoyl-2-elaidoyl *sn*-glycero-3-phosphatidylcholine (PEPC) in lipid bilayers has revealed that the torsion angles of single bonds next to *trans* olefinic bonds are broadly distributed in the range from −180 to +180°, peaking at the *trans* conformation. As noted in the previous paragraph, the united-atom MD simulation does not describe well the conformation of the single bonds next to the *cis* olefinic bond in POPC lipid [16]. Therefore, we suspected that united-atom MD simulations would not produce the conformations of the single bonds next to *trans* olefinic bonds, as well as other significant properties (*e.g.*, order parameters and areas per lipid), of mono-*trans*-unsaturated lipids in lipid bilayers [25]. More modern united atom force fields had been developed and had shown to well predict the structure around the cis double bond [29–31].