Molecular Dynamics Investigation of Bond Ordering of Unsaturated Lipids in Monolayers

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Abstract. Molecular dynamics simulations of three model lipid monolayers of 2,3-diacyl-D-glycerolipids, that contained stearoyl (18:0) in the position 3 and oleoyl (18:1 ω 9cis), linoleoyl (18:2 ω 6cis), or linolenoyl (18:3 ω 3cis) in the position 2, have been carried out. The simulation systems consisted of 24 lipid molecules arranged in a rectangular simulation cell, with periodic boundary conditions in the surface plane. 1 nanosecond simulations were performed at $T = 295$ K. C-C and C-H bond order parameter profiles and the bond orientation distributions about the monolayer normal have been calculated. The relation of the distributions to the order parameters was analyzed in terms of maxima and widths of the distributions. The cis double bond order parameter is found to be higher than those of adjacent single C-C bonds. The widths of the two distributions of C-H bonds of the cis double bond segment in di- and triunsaturated molecules are much smaller than that obtained for methylene group located between the double bonds. The bond orientation distribution function widths depend on both the segment location in the chain and the segment chemical structure.

Key words: Order parameter, Orientation distribution functions, Unsaturated lipids, Monolayers, Biomembranes, Molecular dynamics simulation.

1. Introduction

The basis of biomembranes is provided by a bilayer consisting of phospholipids which may differ both in the number of carbons and in the number and location of double bonds. Investigations of the disorder in unsaturated lipid bilayers and monolayers are of great interest because such systems are models for biomembranes: unsaturated lipids are common and important components of biomembranes. An understanding of the structure and dynamics of membrane systems is important to an understanding of their properties and function [1–4]. It should be pointed out that in an overwhelming majority of experimental data on lipid order parameters, hydrocarbon chains of the lipids are fully saturated (see, for instance, references in [5–17]). In contrast, the data on unsaturated hydrocarbon chain order parameter profiles of lipids are scant or lacking [18–24]. Membrane systems have been subjects of intense theoretical study over the past years (e.g., [25–30]). Computer

Figure 1. Chemical structure of model molecule of 2-linoleoyl-3-stearoyl-D-glycerolipid (18:0/18:2 ω 6cis) with the nomenclature and atom numbering according to [52]. The head group R was treated as an effective sphere. In the atom numbering, the first numeral (2 or 3 in C2*k*, C3*k*; $k = 1, 2, \dots, 18$) refers to the fatty acyl chains linked to the glycerol carbon atoms C2 or C3 respectively; k is acyl carbon atom number. The double bonds of the chain 2 are located between a) carbon atoms 9 and 10 in 18:0/18:1 ω 9cis molecule, b) carbon atoms 9 and 10, 12 and 13 in 18:0/18:2 ω 6cis molecule, c) carbon atoms 9 and 10, 12 and 13, 15 and 16 in 18:0/18:3 ω 3cis molecule.

simulation can provide the most detailed information for the conformational behavior of such systems (for reviews see, e.g., [31–42]). There are several computer simulation studies of unsaturated monolayers and bilayers [43–51].

In this paper, results of a molecular dynamics study of three monolayers consisted of model lipid molecules, 18:0/18:1 ω 9cis (2-oleoyl-3-stearoyl-D-glycerolipid, using the nomenclature of [52]), 18:0/18:2 ω 6cis (2-linoleoyl-3-stearoyl-D-glycerolipid) and 18:0/18:3 ω 3cis (2-linolenoyl-3-stearoyl-D-glycerolipid), are presented. The C-C and C-H bond order parameters and orientation distribution functions of the bonds with respect to the monolayer normal were calculated.

The goal of the investigation performed was the elucidation of the difference in bond ordering properties of the lipid hydrocarbon chains of the three monolayers, especially that of the double bond regions. All the double bonds of the unsaturated chains (Δ 9 in 18:1 chain, Δ 9, 12 in 18:2 and Δ 9, 12, 15 in 18:3) are comparatively far removed from the monolayer interface. To decrease the total computer time for the simulations of the three systems, the molecule head group internal structure was ignored, and the monolayer interface was modeled by a flat surface. Computer simulations of the last decade [31–51] show that it has been possible to recognize the distinguishing qualitative features of bond ordering of membrane structures using different (and relatively simple) models with different force fields and parameters.

2. Theoretical Model

The chemical structure (with the atom numbering) of 18:0/18:2 ω 6cis molecule by way of example is shown in Figure 1. The tails of the lipid molecules were treated in accordance with their real chemical structure, a polar head group of the molecules was treated as an effective sphere with a Van der Waals interaction with the chain atoms. All hydrogen atoms were included explicitly in the calculations except the two hydrogens of C1-group in Figure 1 ($C1 \equiv CH_2$).

Table I. Bond-stretching parameters (Equation (3))

K_l , kcal mol ⁻¹ Å ⁻²	l_0 , Å	Bond	
		Atom1	Atom2
320.0	1.333	C	C
160.0	1.535	CT	CT
140.0	1.507	C	CT
200.0	1.330	C	OS
300.0	1.220	C	O
140.0	1.440	CT	OS
170.0	1.085	C	H
170.0	1.100	CT	H
160.0	1.535	CT	C1
50.0	5.500	C1	R

Table II. Angle-bending parameters (Equation (4))

K_θ , kcal mol ⁻¹ rad ⁻²	θ_0 , deg	Angle		
		Atom1	Atom2	Atom3
50.0	109.5	X	CT	X
50.0	120.0	X	C	X
50.0	12.0	X	OS	X

The energy U of a monolayer was calculated as

$$U = \Sigma U_{intra} + U_{inter} + \Sigma U_{surf} \quad (1)$$

the sums over all the lipid molecules in the monolayer. The total intramolecular energy of the molecule, U_{intra} , was calculated as the sum of the bond-stretching energy ΣU_b , the angle-bending energy ΣU_a , the torsional motion energy ΣU_t , the out-of-plane energy (only for planar groups of the molecule – the double bonds and the carbonyl groups) ΣU_{oop} , the energy of nonbonded interactions $\Sigma \Sigma U_{nb}$:

$$U_{intra} = \Sigma U_b + \Sigma U_a + \Sigma \Sigma U_{nb} + \Sigma U_t + \Sigma U_{oop}. \quad (2)$$

The constituents of the energy U_{intra} were taken in the form of

$$U_b = K_l \cdot (l - l_0)^2, \quad (3)$$

$$U_a = K_\theta \cdot (\theta - \theta_0)^2, \quad (4)$$

$$U_t = W_\varphi [1 + \lambda \cdot \cos(n_0 \cdot \varphi)], \quad (5)$$

Table III. Torsion parameters (Equation (5))

W_φ , kcal mol ⁻¹	n_0	Torsion				λ
		Atom1	Atom2	Atom3	Atom4	
0.167	3	X	CT	CT	X	+1
0.167	3	X	CT	C	X	-1
7.500	2	X	C	C	X	-1
2.250	2	X	C	OS	X	-1
0.130	3	X	CT	OS	X	+1

Table IV. Parameters of nonbonded interactions (Equation (7))

ε_{ij} , Kcal mol ⁻¹	σ_{ij} , Å	Atom type
0.029	2.363	H
0.040	3.653	C
0.040	3.653	CT
0.412	2.626	O
0.412	2.626	OS
0.100	3.920	C1
0.010	7.127	R

$$U_{oop} = W_v \cdot [1 - \cos(2 \cdot \varphi)], \quad (6)$$

$$U_{nb} = U_{LJ}(r_{ij}) - U_{LJ}(R_{int}), \quad r_{ij} < R_{int}, \quad (7)$$

$$U_{nb} = 0, \quad r_{ij} \geq R_{int},$$

where $U_{LJ} = 4\varepsilon_{ij} \cdot [(\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6]$. Here l is the bond length, θ is the bond angle, φ – the torsion angle, r_{ij} is the distance between nonbonded atoms i and j ; ε_{ij} , σ_{ij} are the Lennard-Jones parameters for the atom pairs. Tables I–IV contain the potential parameters for Equations (3)–(5), (7) used in the simulations (notations: CT is carbon in methylene or methyl groups, C – carbon of double bonds, H – hydrogen, OS is ester oxygen, O – carbonyl oxygen, X is arbitrary atom, C1 – united atom group CH₂ in Figure 1, R – head group united atom). The parameters for nonbonded interactions ε_{ij} and σ_{ij} for H, C, CT, O, OS were borrowed from [53]; the rules $\varepsilon_{ij} = (\varepsilon_{ii} \cdot \varepsilon_{jj})^{1/2}$, $\sigma_{ij} = (\sigma_{ii} + \sigma_{jj})/2$ were used; $R_{int} = 10.5$ Å. In the case that atom C has exactly 3 neighbors (Equation (6)), $W_v = 5.0$ Kcal mol⁻¹.

The intermolecular energy U_{inter} (Equation (1)) was taken as the sum of energies over all the intermolecular pairs of atoms, $U_{inter} = \Sigma \Sigma U_{nb}$, where U_{nb} is the energy of nonbonded interactions (7). The surface interaction energy U_{surf} was

$$U_{surf} = \Sigma U_{gphob} + U_{gphil}. \quad (8)$$

ΣU_{gphob} is the sum over all the atoms of the molecule, where

$$U_{gphob} = C_{srb} \cdot [(R_{srb}/Z)^9 - 3 \cdot (R_{srb}/Z)^3 + 2], \quad 0 < Z \leq R_{srb}, \quad (9)$$

$$U_{gphob} = 0, \quad Z > R_{srb},$$

and U_{gphil} is the head atom – surface connection energy,

$$U_{gphil} = (1/2) \cdot C_{bot} \cdot (Z - Z_{bot})^2. \quad (10)$$

Here $C_{srb} = 1.0 \text{ Kcal mol}^{-1}$ is adsorb energy parameter, $R_{srb} = 1.5 \text{ \AA}$ is adsorb energy minimum, (Equation (9)). $C_{bot} = 10.0 \text{ Kcal mol}^{-1}$ is the head atom connection energy parameter, $Z_{bot} = 1.5 \text{ \AA}$. Z is z -position of any atom in Equation (9) and that of the head atom in Equation (10). Position of the wall is $Z_0 = 0.0$. $Z > Z_0$, no water molecules (or other solvent molecules) were present explicitly.

The simulation monolayers consisted of 24 lipid molecules arranged in a rectangular simulation cell, with periodic boundary conditions in the plane of the monolayer surface (in X , Y directions; the normal is an inward-directed Z axis pointed from the monolayer surface). The systems were coupled to an external temperature bath of 295 K and surface pressure bath of 10 dyn cm^{-1} in X and Y directions (according to [54]). The equations of motion were integrated by using leap-frog Verlet algorithm [55], the simulation time step was 1 fs. Atom masses were 1 a.w.u. for atom H, 12 for C, 14 for the group CH_2 , 16 for atom O, and 150 for the head group R. After the monolayers had reached equilibrium state (~ 300 -ps simulations), a molecular dynamics run of 1000 ps for each monolayer was carried out. The average areas per model lipid molecule over the simulations were $48.8 (\text{\AA})^2$ in 18:0/18:1-monolayer, $51.6 (\text{\AA})^2$ - in 18:0/18:2- and $53.0 (\text{\AA})^2$ - in 18:0/18:3-monolayer. Snapshots of the conformations of the monolayers observed in the course of the simulations are shown in Figure 2.

C-C and C-H order parameters S_{CC} , S_{CH} given by

$$S = (1/2) \cdot (3 \langle \cos^2 \beta \rangle - 1), \quad (11)$$

where β is the angle between the bond and the monolayer normal n , were calculated (the averaging is done over all molecules in the monolayer and over the time). Also, bond orientation distribution functions $\rho_{CC}(\beta)$, $\rho_{CH}(\beta)$ for all the C-C and C-H vectors of the lipid molecule tails in each monolayer were calculated. The sense of the vector n coincides with Z -axis; vector $C_i - C_j$ is i to j , $i < j$; vector C-H is C to H; $0 \leq \beta \leq 180^\circ$.

3. Results and Discussion

Order parameters. The profiles S_{CC} and $-S_{CH}$ of the chains in the monolayers are presented in Figures 3, 4. Figure 3 shows marked differences between odd and even

Figure 2. Side views of the monolayer 18:0/18:1 ω 9cis (A), 18:0/18:2 ω 6cis (B) and 18:0/18:3 ω 3cis (C) structure observed in the course of the MD-simulations.

order parameters S_{CC} (odd-even effect) for saturated and unsaturated hydrocarbon chains of the three lipid monolayers investigated. The effect for saturated chains is well-known [16, 56]: this is because the rotations of the CH_2 -groups about their local axes are anisotropic [56]. The difference in behavior and properties of unsaturated lipids is that the S_{CC} odd-even effect in 18:2-, 18:3-chains changes ‘sign’ between double bonds. The cis double bond $\text{C}=\text{C}$ parameters S_{CC} are more high than those of adjacent single $\text{C}-\text{C}$ -bonds. This is consistent with the mean-field cal-

Figure 3. Order parameter S_{CC} (Equation (11)) profiles of the lipid hydrocarbon chains of the monolayers as determined from the MD-simulations. The arrows indicate the double bonds. C-C bond number k of the fatty acyl chains is the bond between carbons k and $(k + 1)$, i.e., between $C2k$, $C2(k + 1)$ or $C3k$, $C3(k + 1)$, Figure 1.

culations [30] and the MD simulations [45] for $18:1\omega9cis$, our MD simulations [50, 51] for $20:4\omega6cis$ and $22:6\omega3cis$ lipid chains. The order parameter $-S_{CH}$ profiles (Figure 4) show that the values of $-S_{CH}$ of double bond carbons significantly differ from one another: dips in the values are observed near the locations of carbons of double bonds. It is in good agreement with the available experimental data ($|S_{CD}|$) and those of computer investigations on bilayers for acyls $18:1\omega9cis$ [5, 6, 18, 20, 21, 30, 43–47] and $18:2\omega9cis$ [22, 44]: the order parameter profile shapes are quite similar to ours. The profiles $-S_{CH}$ of saturated chain 18:0 (all the values of S_{CH} are negative) exhibit a ‘plateau’ (Figure 4) which is also observed in experiments [5–15]. The local picture of bond ordering is difficult to obtain exactly from order parameter (except two cases: when $S = 1$, the bond is parallel to the normal n , when $S = -0.5$, the bond is perpendicular to it). It should be pointed out that the

Figure 4. Hydrocarbon chain order parameter $-S_{CH}$ (Equation (11)) profiles of the computed monolayers and the experimental variation of the deuterium order parameter, $|S_{CD}|$, with the segment position in the region of the double bonds for the oleoyl chain (18:1 ω 9cis)exp of bilayers of 2-palmitoyl-3-oleoyl-D-glycero-1-phosphocholine (at 300 K) [6, 18] and the isolinoleoyl chain (18:2 ω 9cis)exp of 2-palmitoyl-3-isolinoleoyl-D-glycero-1-phosphocholine (at 313 K) [22]. The arrows indicate the double bond positions (for the acyl carbon atom numbering see Figure 1 caption).

parameter S values of some bonds turned out to be near zero (e.g., S_{CC} of the 13-th bond of 18:2 chain in Figure 3, and $-S_{CH}$ of the 11-th carbon of 18:3 chain in Figure 4). If the bonds do not show any preferred orientation, so $S = 0$. However, an S that equals 0 does not necessarily mean that the bond orientation distribution is full isotropic: a value of $S = 0$ can result from different distributions.

Distribution functions. In the general case bond orientation probability distribution functions $\rho_{CC}(\beta, \phi)$, $\rho_{CH}(\beta, \phi)$, where the angles β and ϕ are the polar coordinates

Figure 5. Histograms of C-C bond-vector orientation distributions $\rho_{CC}(\beta)$ of the chain 18:3 ω 3cis relative to the computed monolayer 18:0/18:3 ω 3cis normal n ; 1, 2, 3, ..., 17 are C-C bond numbers. Each of the distributions contains 60 calculation points (see text). This enables the histograms to be represented as the reasonably smooth functions.

of the bond-vector with respect to the monolayer normal, allow the detailed description of ordering picture of the C-C and C-H vectors. Since the order parameter (11) depends solely on the angle β between the bond and the normal n , only the β -dependence of the distributions ρ_{CC} and ρ_{CH} was investigated. For computation of the time averages and the distribution functions, configurations of the monolayers were sampled every 250 fs (the trajectory lengths were 1000 ps). The angle β_i

range $0 - 180^\circ$ of the bond i (C-C or C-H) was divided into 60 sectors j of 3° each: $0-3^\circ, 3-6^\circ, \dots, 177-180^\circ$. Then the percentage of j -th sector appearance ($j = 1, 2, \dots, 60$) for the angle β_i was calculated. The functions $\rho_{\text{CH}}(\beta)$ of CH_2 -groups were found by averaging over the two C-H-bonds. Such a sampling and a number of the sectors have made it possible to obtain the reasonably smooth distributions $\rho_{\text{CC}}(\beta)$, $\rho_{\text{CH}}(\beta)$ for all the bonds of the lipid hydrocarbon chains. For example, the distributions $\rho_{\text{CC}}(\beta)$ calculated for 18:3 ω 3cis-chain are presented in Figure 5. All the distributions of the three monolayers turned out to be monomodal, as in Figure 5. Following the method used in our reports on the intramolecular ordering [57–59], the relations of all distributions $\rho(\beta)$ to the parameters S were analyzed in terms of angles β^{max} and widths of the distributions $\delta\beta$. Here β^{max} is the angle β , when $\rho(\beta^{\text{max}}) = \text{maximum}$. Thus β^{max} is preferred orientation of the bond, a geometric factor of bond ordering. The width of $\delta\beta$ corresponds to half-height $\{\rho(\beta^{\text{max}})\}/2$ of the distribution, therefore $\delta\beta$ is a factor of orientation fluctuations. It is obvious that replacement of n by $-n$ yields $\rho(\beta) \rightarrow \rho(180^\circ - \beta)$, hence $\delta\beta$ remains unaffected and β^{max} is substituted by $180^\circ - \beta^{\text{max}}$ for all the distributions, that leaves the physical meaning of the factors β^{max} and $\delta\beta$ invariant.

The results of the treatment of data for the distributions $\rho_{\text{CC}}(\beta)$ are presented in Figures 6, 7, the same of $\rho_{\text{CH}}(\beta)$ – in Figures 8, 9. The angles $\beta_{\text{CC}}^{\text{max}}$ of the double bonds C=C were determined at 20.4° for 18:1 chain, 24.3° and 24.5° for 18:2, and 24.3° , 29.2° and 35.4° for 18:3, Figure 6 – these angles are of small value, whereas the average angles $\langle\beta\rangle$ of these double bonds were 28.7° for 18:1 chain, 35.2° and 41.7° for 18:2, and 40.7° , 50.0° and 60.6° for 18:3. According to MD simulations [45], the angles $\langle\beta\rangle$ for the C=C bond in 18:1 chain are 22.7° at $A = 46.3 (\text{\AA})^2$ (A is the average area per lipid head group) and 38.4° at $A = 65.5 (\text{\AA})^2$. The angles $\beta_{\text{CC}}^{\text{max}}$ of the previous and the following C-C bonds (no. 8, 10 in 18:1; 8, 10, 11, 13 in 18:2; 8, 10, 11, 13, 14, 16 in 18:3) are 2–3 times higher than those for the double bonds. The fluctuation factor $\delta\beta_{\text{CC}}$ values of C=C double bonds are much less (the distribution functions are more narrow) than that obtained for adjacent single C-C bonds (Figure 7). Consequently, high values of the double bond order parameters S_{CC} (Figure 3) are due to not only the geometric factor (small angles of the most probable bond orientations) but also the fluctuation factor (small bond distribution function widths).

The two $\delta\beta_{\text{CH}}$ values of C-H bonds of the double bond carbons in the chain 18:1 (59.4° and 61.6° for carbons 9, 10 in Figure 9) are greater than for adjacent CH_2 -groups (42.3° and 48.5° for carbons 8, 11 in Figure 9). The same is observed in the 18:2 chains to the left and right of the double bond carbons, but the $\delta\beta_{\text{CH}}$ value of CH_2 -group located between the double bonds (see carbon 11 in 18:2, Figure 9) is nearly 2 times higher (113.0°) than that for C-H bonds of double bond carbons ($\sim 59 - 65^\circ$). This broadening effect is also repeated in triunsaturated chain (see carbons 11, 14 in 18:3, Figure 9). According to Figure 8, the values of $|90^\circ - \beta_{\text{CH}}^{\text{max}}|$ for carbons 9, 10 in the chain 18:1 are equal to 24.6° and 28.5° respectively. Therefore, the difference in their $-S_{\text{CH}}$ values (Figure 4) is because

Figure 6. The calculated angle values $\beta_{CC}^{\max}$ which correspond to the C-C bond-vector distribution function maxima $(\rho_{CC}(\beta))_{\max}$ of the lipid hydrocarbon chains of the monolayers. The arrows indicate the double bond positions. Accuracy is within symbol size.

of both the geometric (this contribution dominates) and the fluctuation (see above) factor differences. The values of $|90^\circ - \beta_{CH}^{\max}| = 13.1^\circ$ and 40.1° for carbons 9, 10 in the chain 18:3 (Figure 8), whereas $\delta\beta_{CH} = 57.8^\circ, 59.1^\circ$ respectively (Figure 9), so the dip in their $-S_{CH}$ is due to a pure geometric effect. In contrast, in the chain 18:2 the magnitude $|90^\circ - \beta_{CH}^{\max}| = 14.5^\circ$ and 14.7° for carbons 9 and 11, however, as discussed above, $\delta\beta_{CH} = 59.5^\circ, 113.0^\circ$ respectively: the difference in the appropriate $-S_{CH}$ values is due to a pure fluctuation effect.

Figure 7. The calculated values of C-C bond-vector distribution function widths $\delta\beta_{CC}$ which correspond to half-heights $\{\rho_{CC}(\beta_{CC}^{\max})\}/2$ of the distributions, for all the chains of the computed monolayers. Symbols are the same as in Figure 6.

The $\delta\beta_{CC}$, $\delta\beta_{CH}$ values of the 18:0 chain of the monolayers turned out to be increased nearly monotone toward the chain ends. The 18:0 angles $\beta_{CC}^{\max}$ lie in the range ~ 32 to 40° , $\beta_{CH}^{\max}$ – in $\sim 87 - 93^\circ$, and odd-even effect is observed.

It should be emphasized that the fluctuation factors $\delta\beta_{CC}$, $\delta\beta_{CH}$ depend on both the segment location in the chain (carbon number) and the segment chemical structure, cf. all the profiles in Figures 7, 9. This is inconsistent with the conclusion of Reference [18] that the segmental fluctuations (in bilayers of 1-palmitoyl-2-oleoyl-

Figure 8. The calculated angle values $\beta_{CH}^{\max}$ which correspond to the C-H bond-vector distribution function maxima $(\rho_{CH}(\beta))_{\max}$ of the lipid hydrocarbon chains of the three monolayers. The arrows indicate the double bond positions. Accuracy is within symbol size.

sn-glycero-3-phosphocholine, 16:0/18:1-PC) are not dependent on the segment geometry but are determined by the distance of the segment from the lipid-water boundary [18]. Our findings, on the other hand, are in line with the results of intramolecular bond order investigations of the isolated unsaturated chains in the molecule-fixed coordinate system by Monte Carlo method [57–59]. The values of $\beta^{\max}$ and $\delta\beta$ are useful in most cases in evaluation of geometric and fluctuation contributions to the order parameter S . Defining these properties is a necessary

Figure 9. The calculated values of C-H bond-vector distribution function widths $\delta\beta_{CH}$ which correspond to half-heights $\{\rho_{CH}(\beta_{CH}^{\max})\}/2$ of the distributions, for the chains of the computed monolayers. Symbols are the same as in Figure 8.

step to gaining a more complete understanding of unsaturated and polyunsaturated lipid hydrocarbon chains significance.

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