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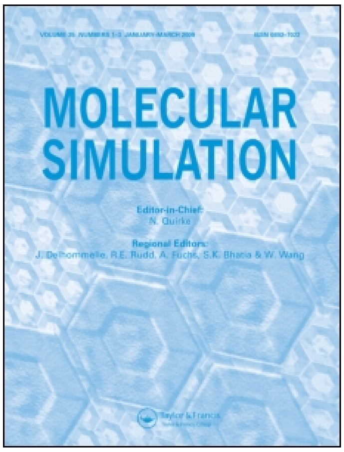

Molecular Simulation

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MOLECULAR DYNAMICS SIMULATION OF MODEL LIPID MEMBRANES: STRUCTURAL EFFECTS OF IMPURITIES

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The gel to fluid phase transition or ordered to disordered phase transition observed in biological membranes are simulated by using constant energy Molecular Dynamics. The surface part of the membrane is modelled as a two-dimensional matrix formed by the head groups of the phospholipid molecules. Head molecules which are modelled as three spheres fused with three force centers, interact with each other *via* van der Waals and Coulomb type interactions. The -so called- impurity or foreign molecule embedded in the surface represents the protein type molecule which is present in biological membranes and control its activity. It is modelled as a pentagon having one force centers in each corner. It also interacts with the surface molecules again *via* van der Waals and Coulomb type interactions. The surface density is kept constant in the simulations of the systems with or without impurity. Structural and orientational changes due to impurity were observed and proved by monitoring two-dimensional order parameter. It has been shown that melting of the surface or breakage of the ordering of the surface molecules becomes easier and ordered to disordered phase transition temperature was lowered by 100 K if the impurity is present.

Keywords: Molecular Dynamics Simulation; Lipid membranes; Gramicidin-A; Biological membranes

1. INTRODUCTION

Biological membranes are very thin bimolecular layers made up lipids molecules. The major components of isolated membranes are phospholipids. Two-dimensional matrix of these phospholipid bilayers are interrupted and coated by different kinds of proteins and other molecules like sugars, *etc.* [1]. This dynamic organization of the membrane makes it sensitive to both physical and chemical perturbations. Local changes in organization result in relevant changes in the function of the entire system [2].

Phospholipid molecules belong to a general group of zwitterionic amphiphilic molecules. In an aqueous or in a nonaqueous environment these amphiphiles self-associate into different aggregates. They have polar head groups which are hydrophilic part of the molecule and nonpolar tail(s) which are the hydrophobic part of the molecule. One can see clear-cut difference between head and tail parts. By this way, head groups of the phospholipid molecules form a two dimensional surface where the most of the interesting chemistry occurs. The most important molecular source of the headgroup hydrophilicity is the electrostatic interactions between the local charges on the zwitterion which consists of a positive quaternary ammonium group and a negative phosphate group and uncharged ester group. Through the ester linkages, head is connected to the tail part of the phospholipid molecules. Tail part of the molecules consists of one or more long hydrocarbon chains made up 15–30 carbon atoms in each chains. For different phospholipids, the positively charged group of the head changes. Depending on the hard sphere radius for the positive center, the strength of electrostatic interactions with the negative center may vary. This might be the source of the different physicochemical properties of the lipids [3]. The motion of the head groups is slower by 3–4 orders of magnitude than tail groups. The second type molecules which are present in biological membranes are proteins. They are not the major component of the membranes but their interactions with lipids and the other molecules are very important in terms of the functions of the membranes. The proteins are grouped in two classes: integral membrane proteins, which traverse the bilayer and primarily interact with the bilayer through hydrophobic forces; and peripherally associated with the lipid bilayer and primarily interact with the bilayer through polar (electrostatic and hydrogen bond) interactions. In either case, the proteins ‘float’ in a fluid sea of lipid molecules. Gel to fluid transition characteristics of bilayers are appreciably modified in the presence of proteins and other lipids. They sometimes behave like solutes in a bilayer which isothermally perturb the local organization without disrupting the topography. Most solutes incorporated in bilayers alter the thermotropic transition characteristics. In general, the effect of additives is much more pronounced on the pretransition than it is on the main transition.

Most nonpolar or amphipathic solutes lower T_m, decrese enthalpy and broaden the temperature range over which the transition occurs.

2. MODELLING

Model membrane systems have been developed primarily to provide simplified versions of biological membranes, which allow the properties of individual components to be studied in detail and computations to be performed in a reasonable time scale. Model systems have provided a great deal of information on the conformations of lipids in membranes. This has led to many insights concerning the roles of lipids in membranes and its short range and long range interactions with the other molecules around [4–6].

In our model, a phospholipid head group is modelled as a rigid-body which consists of three spheres fused together (Fig. 1). Each sphere represents the real volumes of the choline $(N(CH_3)_4)^+$, phosphate $(PO_4)^-$, and the ester groups in real phospholipid molecule (Fig. 2). The relative positions of the center of masses of the groups are taken from the 3-dimensional picture of a real phospholipid molecule. These spheres having positively charged, negatively charged and uncharged force center in the middle, are named as A, B and C respectively. The vibrational motion of the

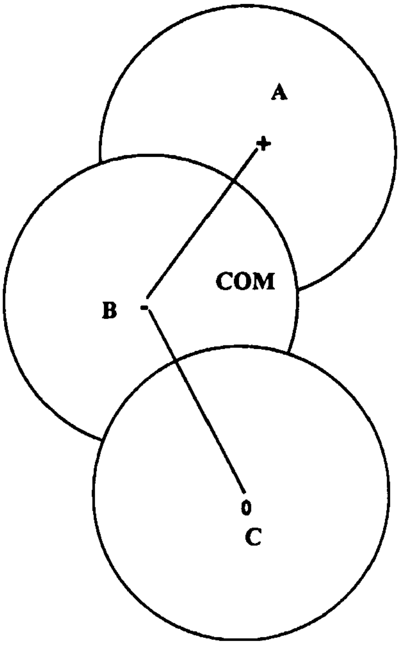

FIGURE 1 Model phospholipid head molecule (COM: Center Of Mass).

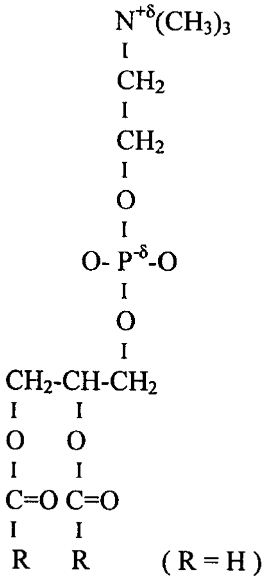

FIGURE 2 Phospholipid head group.

rigid bodies is forbidden whereas the translational motion on two-dimensional simulation box and the rotational motion around the z-direction which is perpendicular to the molecular plane, are allowed. The rotational plane contains the center of mass of the head group. Hence each head molecule has three degrees of freedom described by the x and y coordinates of the center of mass and the rotation angle in x-y plane with respect to an arbitrary vector in the plane. Initially, the center of masses of 120 molecules are placed on the lattice points of a (1,1,1) plane of an fcc lattice. The initial angular coordinates of each molecule are chosen randomly. Three centers of the head groups have different z coordinates but they are kept unchanged during the course of the simulation. Periodic boundary conditions are applied in x and y directions. Box sizes are optimized as $x_{box} = 96.3\,Å$ and $y_{box} = 100.1\,Å$ to give number density of $0.01245\,Å^{-2}$. Initial velocities of the surface molecules are set to be zero. Interaction potentials are chosen to be the sum of Lennard-Jones and Coulomb potentials.

$$V_{ij} = 4\varepsilon[(\sigma/r_{ij})^{12} - (\sigma/r_{ij})^{6}] + (\delta_i\delta_j e^2/r_{ij}) \qquad (2.1)$$

where e is the elementary charge. First part in the potential expression represents the nonpolar interactions whereas the second part represents the interaction between charged particles. NVE simulations of the two-dimensional surface consisting of 120 model phospholipid head molecules are carried out and reported previously [7]. Structural changes as a function of potential parameters like δ, ε and temperature are studied intensively. Here, our aim is to analyze the effects of a bulky group on a membrane surface. For this reason, a model molecule resembling Gramicidin-A is chosen and placed onto the two-dimensional matrix of model head groups. Gramicidin-A molecule is a neutral linear pentadecapeptide (polypeptide). It is a biologically very important molecule, known to be one of the best characterized ion channel. Transmembrane channels are formed by its dimer which gives rise to a 28 Å- long channel of about 4 Å internal diameter. There are several Molecular Dynamics Simulation studies on such channels where the diffusion or ion transport phenomena can be explained successfully [8].

In this study, Gramicidin-A molecule is modelled as a pentagon (Fig. 3) having a point charge and force center at each corner. This bulky molecule

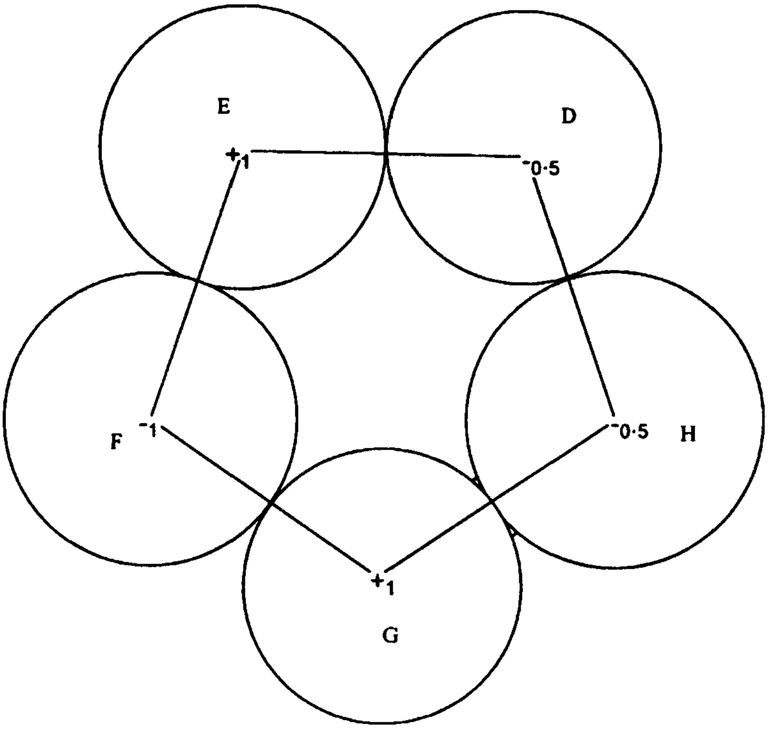

FIGURE 3 Model Gramicidin-A molecule.

is also a rigid body. Each force center on the pentagon interact with the each force center on the head molecules under the same interaction potential given above. After placement of this molecule, the number of head molecules are lowered in order to keep the surface density constant. Initially, it is put in the middle of the surface, then allowed to translate and rotate on the surface by interacting with the head molecules *via* the same potential function given above. Orientational order in model phospholipid and Gramicidin systems was observed as a function of system or structural parameters and temperature and was compared to the pure systems.

3. RESULTS

Throughout the simulations, the potential parameter σ, the hard sphere diameters of groups is kept constant as 6 Å. The other potential parameters ε and charge ($q = \delta e$) and the temperature are changed accordingly to scan all the parameter space. Model parameters for phospholipids and Gramicidin are given in Table I. It has been shown that the parameters are related to each other because of scaling properties of the total Hamiltonian of the system. Two simulations (1) and (2) follow the equations:

$$T_1\varepsilon_2 = T_2\varepsilon_1; \quad \delta_1^2\varepsilon_2 = \delta_2^2\varepsilon_1 \tag{3.1}$$

We carried out NVE Molecular Dynamics Simulations. Newton equations are solved by sixth order Gear algorithm with time steps of 10 fempto seconds. Equilibration takes 50000 time steps and another 10000 steps are needed to collect data for further analysis.

A variety of systems with and without model Gramicidin-A type molecule, are studied in terms of two-dimensional order parameter which

TABLE I Model parameters

Group	*Mass (amu)*	*Charge (esu)*	$\varepsilon(10^{-21} J)$	σ (Å)
A	78	$+\delta$	ε	6
B	103	$-\delta$	ε	6
C	75	0	ε	6
D	150	$-\delta/2$	ε	6
E	150	$+\delta$	ε	6
F	150	$-\delta$	ε	6
G	150	$+\delta$	ε	6
H	150	$-\delta/2$	ε	6

is derived from three-dimensional order parameter [9], and denoted by S which is given as:

$$S(r, \Delta r) = \sum_{k=1}^{M} S_k(r, \Delta r)/M \tag{3.2}$$

where $S_k(r, \Delta r)$ is the distance-dependent order parameter for the k-th time step and it is defined as

$$S(r, \Delta r) = \langle 2\cos^2\varphi_{ij} - 1\rangle_{r,\Delta r} \tag{3.3}$$

φ is the angle between the normal vector of a central dipole and the corresponding vector of other dipoles. Average is taken starting from a center i, over all molecular head groups j located in a circular shell within a two dimensional volume $V(r, \Delta r) = 2\pi r\Delta r$, and averaged over M independent time steps. S changes between 0 (for a completely disordered system) and 1 (for a completely ordered system where the dipolar vectors are either parallel or anti-parallel).

First system analyzed is a disordered one where the temperature (T = 300 K) and the charges on the dipoles ($\delta = 0.65$) are kept constant. The van der Waals parameter ε is changed from 1.0×10^{-21} J to 10.0×10^{-21} J. In Figure 4, order parameter *versus* ε is plotted. Solid curve represents the pure system whereas dashed curve represents the impure system. As the strength of nonpolar interactions is increased, the system goes from disordered liquid type phase to more ordered solid type phase. This transition is more pronounced for the pure system and at $\varepsilon = 6.0 \times 10^{-21}$ J, we observe sharp increase in the order parameter. When we look at the trajectory plots of these system, it is notable that this sharp increase in order parameter is because of the sudden clustering of the surface because of the high ε. Rather this weak transition is observed for the impure system and clustering of the surface molecules begins at higher ε regime.

In the second system, again the effect of changing ε between 1.0×10^{-21} J to 10.0×10^{-21} J is observed but this time the charges on the dipoles are increased from 0.65 to 1.0 while the temperature is still the same. Here, dipolar and nonpolar effects on the interactions of the particles compete. For the low ε values, both systems are very well ordered because of the high dipolar charges and when the ε is increased order is broken at around $\varepsilon = 8.0 \times 10^{-21}$ J. This can be better seen in Figure 5 where order parameter *versus* ε is plotted. This is the point that the effect of ε cancels the the effect of charge. From that point, upon further increase of ε leads clustering of the molecules again, hence small increase in order parameter for the pure system

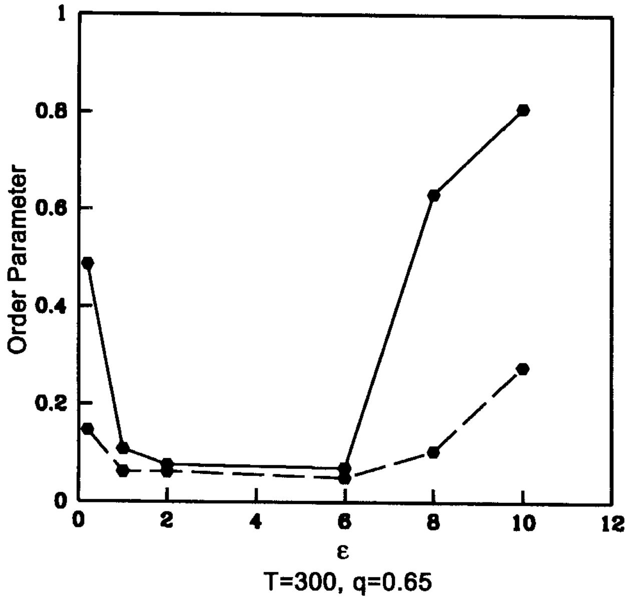

FIGURE 4 Change of order parameter (S) with ε. T = 300 K and q = 0.65. Dashed curve represents the impure system and solid curve represents the pure system.

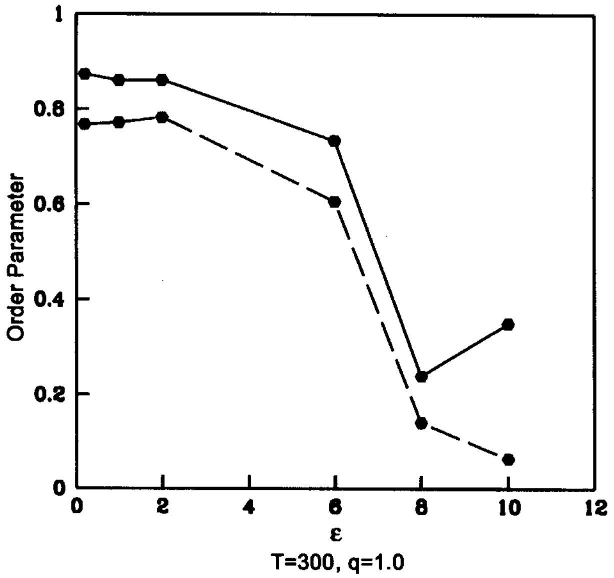

FIGURE 5 Change of order parameter (S) with ε. T = 300 K and q = 1.00. Dashed curve represents the impure system and solid curve represents the pure system.

is observed. It is clearly seen that the presence of an foreign molecule does not create significant differences structurally although the order parameter of impure system is always lower than the order parameter of pure system for all ε values.

In the third system, very small ε value is chosen ($\varepsilon = 0.2 \times 10^{-21}$ J) to see the effect of dipolar interactions. While temperature (T = 300 K) and ε are constant, δ is changed from 0.25 esu to 1.00 esu by the increments of 0.25 units. Both systems shows transition at $\delta = 0.65$. The transition is very sharp and strong for the pure system implying that it is a disordered to ordered or in other words liquid to solid type transition. But for the impure system, this transition is weak and the system goes from a disordered phase to a less disordered phase. For the higher charge values, the order parameter of the pure system is around 0.9 whereas the order parameter of impure system is around 0.2 (Fig. 6).

Finally, the last system where the dipolar interactions are very strong and van der Waals interactions are very weak, *i.e.*, $\delta = 1.0$ and $\varepsilon = 0.2$. The effect of temperature is analyzed by changing the temperature from 100 K to 800 K. At 100 K, both systems shows very ordered solid type structure. As

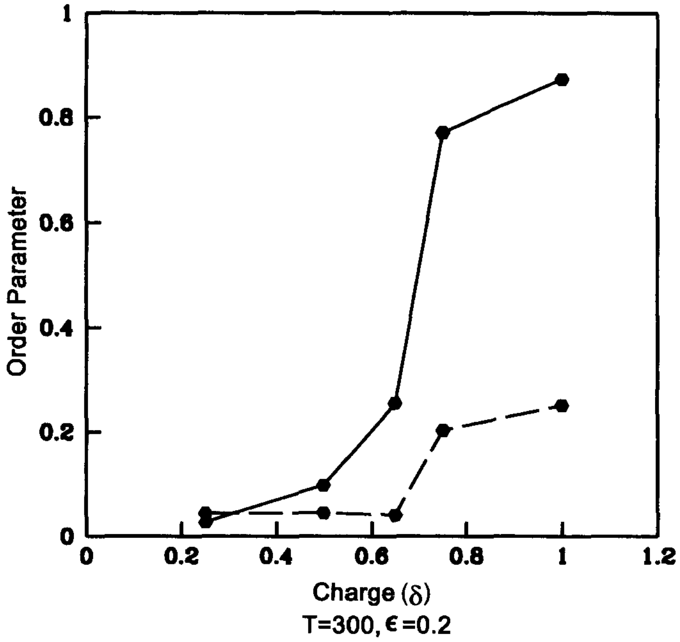

FIGURE 6 Change of order parameter (S) with δ. T = 300 K and $\varepsilon = 0.2$. Dashed curve represents the impure system and solid curve represents the pure system.

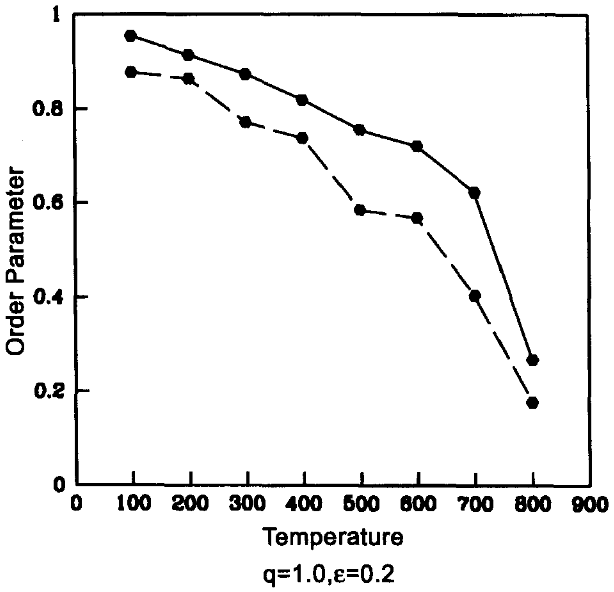

FIGURE 7 Change of order parameter (S) with T. $\varepsilon = 0.2$ and $q = 1.00$. Dashed curve represents the impure system and solid curve represents the pure system.

the temperature is increased to 500 K, impure system starts to melt and at around 600 K, pure system starts to melt. The plot of order parameter *versus* temperature is given in Figure 7. As it can be seen from the plot, the melting temperature or the temperature at which the systems go from solid type structure to liquid type structure is lower for the system having impurity.

4. SUMMARY

Simulation techniques are widely used with model liquid systems of hard spheres having dipoles [10] for the investigation of orientational ordering. Here, we applied Molecular Dynamics Simulation technique to study the surface dynamics of pure and impure model membrane systems. The techniques used for the generation of model membranes, and the results derived from model membrane studies, have played a direct role in obtaining some information related to the molecular interactions between membrane and its elements like proteins and their affects on the melting temperature of the two-dimensional membrane surface. It was observed that the presence of an impurity, lower the melting temperature of the surface by

100 K. By introducing a Gramicidin type bulky model molecule to a totally homogeneous matrix made up model phospholipid head groups, we break local ordering of the surface molecules at least in the vicinity of the foreign molecule. The system becomes more disordered and the order is broken easily at lower temperatures.

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