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Monte Carlo studies of lipid / water interfaces

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The results of a series of numerical simulations of the aqueous interface near several types of lipid bilayer headgroups are presented. The Monte Carlo method was used to study 172 water molecules located between two lipid bilayers separated by 24.5 Å. The types of headgroups used in the studies include phosphorylcholine, -ethanolamine and -serine. The quantities calculated were molecular density, dipolar orientation and number of hydrogen bonds as functions of the distance from the interfacial regions. The data point out important differences in the organization of the interfacial water for each of the three different lipids.

Introduction

The interface between the cell surface and the surrounding aqueous medium is undoubtedly important in many biological processes, yet this region is extremely difficult to probe experimentally and nearly impossible to accurately model theoretically. Experimental NMR studies of the lipid headgroups [1] and the hydrocarbon chains [2] have been performed and as a result the lipid conformations are reasonably well-understood, but a clear picture of the states of the layers of water nearest the headgroups has not emerged. Theoretical studies of lipid bilayer phase transitions are hampered by the lack of detailed knowledge of the interface because many statistical mechanical models require a contribution from the lipid/water interface (for a review see Ref. 3) to the free energy. The lack of precise calculations or measurements of this contribution forces theoreticians to use phenomenological parameters which cannot be directly tested at this time.

The rapid development of high-speed computers now allows a third approach to the study of complex molecular assemblies, namely numerical simulation. While simulations have been performed for many years on simple physical systems such as monatomic gases [4] it is now possible to study more complex problems such as solutions and interfaces. To this end, several recent numerical studies of aqueous systems with a hydrophobic wall have been carried out [5–8]. The most complete of these is the work of Lee et al. [8], who use the molecular dynamics method to study the density, orientation and hydrogen-bonding profiles of 216 water molecules interacting with each other via the ST2 potential [9] and with a structure-less wall via a Lennard-Jones potential. The authors find that water molecules near the wall prefer orientations in which the molecular dipole vector is within approx. 30° of being parallel to the interface. This appears to minimize the loss of hydrogen bonding in the liquid caused by the wall. Lee et al. also find oscillations in density, induced by the walls, extending approx. 10 Å into the bulk fluid from each wall. In a more complex simulation, Gruen et al. [10] have performed a molecular dynamics study of a mica/water interface. The

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Abbreviations: PC, phosphorylcholine; PE, phosphorylethanolamine; PS, phosphorylserine.

length of this simulation is rather short so that the results are somewhat tentative.

An inert, flat wall is an approximation to a lipid/water interface but much is left out. As a next step, Scott [11] has performed Monte Carlo simulations of an aqueous interface with phosphorylcholine headgroups. In this work, the phosphorylcholine (PC) groups were placed in fixed orientation parallel to two opposite faces of the simulation cell. Four PC groups on each face interacted with 172 water molecules, modeled by the TIPS2 [12] interaction. The potential for the PC-water interaction contained both Van der Waals and Coulombic terms, and was somewhat simplified from a direct atom-by-atom sum of interactions to a sum of terms representing the entire phosphate and choline groups in order to to save computer time. The computations showed that the PC groups influence the water density in a way similar to that found by Lee et al. [8], but they force the water within approx. 7 Å of each wall into closer dipolar alignment than the purely hydrophobic wall of Lee et al. [8] did when the headgroups are all aligned parallel. Very recently, Kjellander and Marcelja [13] have performed molecular dynamic studies of the phosphatidylcholine/water interface using a model for the interface which is different from that of Ref. 11 in that charge is distributed over more of the headgroup molecules. This apparently produces a slightly stronger polarization perpendicular to the interface for the water within 5 Å than was observed in Ref. 11. Kjellander and Marcelja do not report results for the parallel component of the polarization, which are discussed in Ref. 11.

The studies of Scott [11] have now been extended to include phosphorylethanolamine (PE) and phosphorylserine (PS). The purpose of this paper is to present these new results, and to compare the manner in which the different headgroups affect the interfacial water.

Method

The technique used for this work is the Monte Carlo method as described in Ref. 11. The system consists of a rectangular box of dimensions 11.2 Å (x axis) by 19.6 Å (y axis) by 34.7 Å (z axis). Periodic boundary conditions are imposed along the x and y directions and four headgroups are placed at each x-y face of the box. The headgroups are all oriented parallel to the x-y plane and in this study all groups are aligned with parallel dipole vectors (along the $+y$ direction). The atomic positions are generated from the position of the phosphorus atom by successive applications of rotation operators using known bond lengths [14]. The z coordinates of the P atoms at the upper interface are all 2.7 Å, while those at the lower interface are 32.2 Å. The water molecules are confined sterically to an intermediate region about 24.5 Å thick. The simulations involve 172 water molecules interacting via the TIPS2 potential [12]. In this model, each water consists of two positive point charges of magnitude 0.535 e and subtending an angle of 104.5° with the oxygen atom. A negative charge of magnitude -1.07 e is placed on the bisector of this angle, 0.15 Å from the oxygen. The positive charges are 0.9572 Å from the oxygen. The oxygen atom position serves as the origin for a 6–12 Van der Waals potential of the form:

$$V(r) = A/r^{12} - C/r^{6} \quad (1)$$

where $A = 695\,000$ kcal · Å^{12} and $C = 600$ kcal · Å^{6}, so that the full intermolecular potential has the form:

$$V(r) = A/r^{12} - C/r^{6} + \sum_{ij} q_i q_j / r_{ij} \quad (2)$$

where q_i and q_j are the effective charges and r_{ij} is the separation of the point charges on the various atoms. In the computations, a cutoff of 10 Å was used, but within this cutoff the full potential of Eqn. 2 is always used. Each water molecule also interacts with the eight headgroups via Coulomb potentials between the water point charges and point charges of magnitude $+0.5$ e and -0.5 e at the nitrogen and phosphorus positions, respectively. In addition, the phosphorus and nitrogen atoms serve as sources of Van der Waals potentials, the parameters of which depend upon the headgroup being studied. Using only two sites per headgroup saves computer time and does not greatly oversimplify the intermolecular interactions [11]. In this work, all interaction parameters were fixed at prechosen values. Table I lists the values of the charges and the Lennard-Jones energy and length parameters used in the PC, PS and PE simulations. The effects of varying these parameters is mainly one of scale for the results reported here [11].

The standard Metropolis Monte Carlo method was used [15], Systems were initialized in random configurations and equilibrated by passing through 1000–3000 K configurations. Averages were then taken over 1376 K configurations. In the averaging procedure, the system was divided into 29 layers each parallel to the *x*-*y* pane, and averages were calculated for all molecules in each layer. This provides a profile of the calculated properties along the *z* axis. For each simulation, average profiles were obtained for the following quantities: the three components of the TIPS2 molecular dipole moment vector, the quantities $\langle P_z(\cos\theta_{z,xy})\rangle$ where θ_z and θ_{xy} are angles between OH bonds and the *z* axis and the *xy* plane, respectively, (providing a measure of the rotational motions about these axes), the average number of hydrogen bonds per molecule (using −4 kcal/mol as the bond criteria), and the molecular density. All simulations were run on the Oklahoma State University IBM 3081D mainframe machine using the random number algorithm RANF.

Results

PC headgroups

Polarization and density profiles for the PC/water interface were reported in Ref. 11. New data for this interface consist of hydrogen bond profiles calculated for new configurations generated from one of the final runs used in Ref. 11. The average number of hydrogen bonds $n(z)$ in each layer is shown on the dashed line in Fig. 1. The profile is similar to that of Lee et al. [8] in that $n(z)$ drops from the bulk liquid value of about 2 to approx. 1.5 bonds per molecule for the molecules within approx. 2 Å of the surface.

PE headgroups

The hydrogen bonding profile $n(z)$ for PE is shown on the solid curve in Fig. 1 and the profile for the average component of the TIPS2 water dipole vectors parallel to the interface and to the headgroups (the *y* component) is shown in Fig. 2. The PE simulations differ from those for PC only in the Van der Waals radius of the amine group. This radius was set at 1.6 Å, compared to 2.7 Å used for PC (Table I) based upon the relative sizes of molecular models for the amine and choline groups, respectively. The effect of this smaller radius is to allow at least 1–2 water molecules closer access to the positive charge situated at the nitrogen position, and this should affect the orientation and bonding profiles. Fig. 1 shows that the water molecules nearest the PE headgroups have about the same number of hydrogen bonds as those near PC headgroups. Thus, even though it is possible for a few water molecules to closely approach the amine group, this does not affect the average bonding profile. Fig. 2 shows the profile

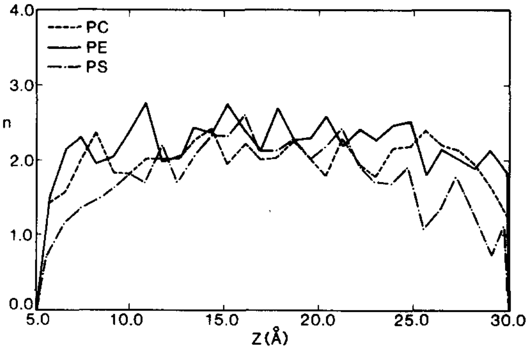

Fig. 1. Plot of $n(z)$, the average number of hydrogen bonds per water molecule, vs. *z*, the coordinate perpendicular to the interface, for PC (dashed line), PE (solid line), and PS (dot-dashed line) interfaces. Slabs used in calculating all profiles are 0.87 Å thick. A cut-off energy of −4.0 kcal/mol was used as the hydrogen bonding criterion [8]. In all figures, the headgroup/water interface, which is not flat, is located at approx. 5 Å (top) and 32.2 Å (bottom).

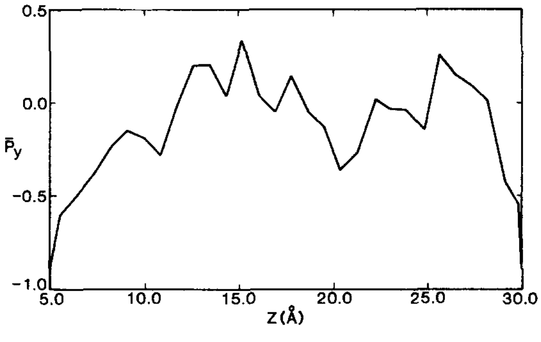

Fig. 2. Plot of $\bar{P}_y(z)$, the average *y* component of the molecular dipole vectors for the water molecules, vs. *z* for a PE interface.

TABLE I

VALUES OF EFFECTIVE CHARGE (q), LENNARD-JONES LENGTH PARAMETER (σ) AND LENNARD-JONES POTENTIAL STRENGTH (ϵ) USED IN SIMULATIONS ($V(r)=\epsilon((\sigma/r)^{12}-(\sigma/r)^{6})$)

Lipid	PO_4 parameters			N parameters			COO parameters [a]		
	q (e)	σ (Å)	ϵ(kcal/mol)	q (e)	σ (Å)	ϵ (kcal/mol)	q (e)	σ (Å)	ϵ (kcal/mol)
PC	−0.5	2.7	3.0	+0.5	2.7	3.0	–	–	–
PE	−0.5	2.7	3.0	+0.5	1.6	3.0	–	–	–
PS	−0.5	2.7	3.0	+0.5	1.6	3.0	−1	2.7	3.0

[a] Used in PS runs only.

of the y component of the average molecular dipole vector. Compared with a similar study for PC [11], the dipolar order is less for water molecules near PE, presumably because the smaller amine group of PE implies a rougher surface for PE than for PC, Also, water molecules nearest the amines will preferentially orient with their negative charges very close to the N atom while the positive charges cannot get as close to the phosphate group. This will disrupt the tendency for parallel dipolar alignment found in the PC studies [11]. The average of the perpendicular component, $\bar{P}_z$, varies between +0.4 and −0.4 in a rapid oscillatory fashion which does not reveal any surface-related polarization effects.

PS headgroups

The PS headgroup is structurally quite different from PC or PE in that, at the methylene group nearest the amine terminus, a hydrogen is replaced by a larger, asymmetrical, and negatively charged carboxyl group. In the simulations, PS is derived from PE by adding a third source of Coulombic and Van der Waals potentials at the site of the carboxyl. The charge strength and Van der Waals parameters are given in Table I. For comparison, runs were also made with the carboxyl charge set equal to zero. The effect of the charged carboxyl group on the properties of the interfacial water are striking. In Fig. 1, the $n(z)$ profile is shown as a dot-dash curve. This profile shows that the water nearest the interface only hydrogen-bonds with an average of one other water neighbor, as compared to approx. 1.5 for PE and slightly less for PC. Furthermore, $n(z)$ does not reach the bulk value until approx. 5 Å from each interface, whereas the profiles for PE and PC reached bulk averages within approx. 3 Å. The polarization profile induced in the water by the charged PS headgroups is shown in Fig. 3. Because the effect is to realign the water dipoles (as compared to the PC case), the average z component of the molecular dipole moment is plotted. The figure shows that there is a strong tendency for the water molecules to align with dipole vectors perpendicular to the interface, with positive charges closest to the headgroups. This produces negative moments at the bottom of the box and positive ones at the top, and there is a fairly smooth crossover between these two antiparallel orientations, with $\bar{P}_z \approx 0$ in the middle. In runs with the charge on the carboxyl set equal to zero, the orientation tendencies of Fig. 3 are not present, but there is also less influence on the y component of $\vec{P}$ than in the PC and PE runs. Presumably, this is due to the asymmetric COO^- at the amine end. The y component of $\vec{P}$ is not

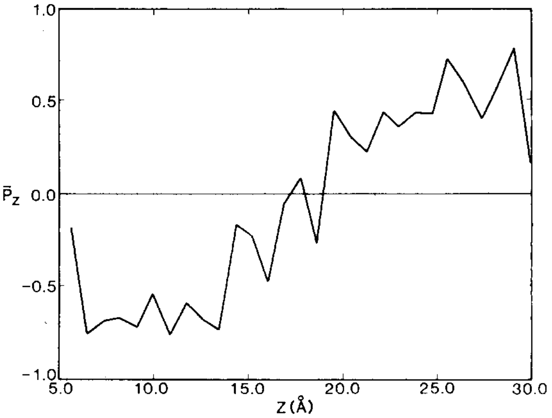

Fig. 3. Plot of $\bar{P}_z(z)$, the average z component of the molecular dipole vectors for the water molecules, vs. z for a PS interface.

strongly affected by this interface, varying between ± 0.3 in a rapid oscillatory fashion.

The $\bar{P}_z(z)$ profile of Fig. 3 is probably an overestimate of the actual polarization induced by the COO^- group for two reasons: firstly, the effective charge of the carboxyl group was set at the full electronic charge. Simulations using a more realistic, reduced, effective charge produce a less striking profile; secondly, in real systems one always has counterions present, and these are not included here. The effect of the counterions will be to shield the Coulombic forces, reducing the magnitude of the induced polarization. The present studies serve to define the conditions under which headgroups can produce long-range effects in the interfacial medium.

In all the simulations reported here, the calculated averages $\langle P_z(\cos\theta)\rangle$ were uniform throughout the cell, showing no interfacial changes in the rotational mobilities if the molecules. $\langle P_z(\cos\theta_z)\rangle$ was always approx. 0, while $\langle P_z(\cos\theta_{xy})\rangle \approx 0.4 \pm 0.1$.

Discussion

The influence exerted upon interfacial water by the various phospholipid headgroups studied is more varied than the influence exerted by a structureless wall [8]. In all cases considered, the fact that the headgroup has a dipolar charge distribution influences the interfacial water markedly. The fact that the magnitudes of this influence vary with the detailed structure of the headgroups is not surprising, and one may expect even greater effects for different headgroups with less symmetry and/or different charge distributions. The simulations consider only local charge effects, in that the effect of COO charges in neighboring cells is not included in the energies of the molecules. It was felt that to include such terms is equivalent to simulating a massively charged interface, which is unrealistic. Thus, in these results, water molecules in the simulation cell are to be considered as shielded from those in neighboring cells.

The implication of this work for the study of biological cell surfaces is that the interactions between the constituents of the cell membrane and the inter- and intracellular water will be rich in variety and complexity. The observed properties of the three systems considered here must ultimately be derived from a thermodynamic free energy, which is minimized for the configurations obtained in the simulations. Unfortunately, the free energy itself is very difficult to compute with any confidence (one must average exponentials which vary rapidly) in the Monte Carlo method. Knowledge of this free energy would be extremely useful in calculating the phase-transition temperatures of lipid bilayers as well as the interbilayer forces in multilamellar liposomes [16–17].

Since free energies are not directly accessible, it is necessary to consider structural differences and similarities in order to understand the various contributions to the thermodynamics of the systems. The present data indicate major differences in the molecular orientation but surprising similarity in the hydrogen bonding patterns at different lipid/water interfaces. If, as seems reasonable, the energetics of the lipid/water interface are dominated by electrostatic contributions (for the water nearest the surface, this was usually the case), then hydrogen bond patterns should be indicators of any substantial structural differences for the different interfaces. Since these patterns are all fairly similar one is forced to conclude that the differences in phase-transition temperatures for lipids having identical aliphatic chains but different headgroups must be in large part due to direct interactions between adjacent headgroups.

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