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Constant Pressure and Temperature Molecular Dynamics Simulation of a Fully Hydrated Liquid Crystal Phase Dipalmitoylphosphatidylcholine Bilayer

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ABSTRACT We report a constant pressure and temperature molecular dynamics simulation of a fully hydrated liquid crystal (L_α) phase bilayer of dipalmitoylphosphatidylcholine at 50°C and 28 water molecules/lipid. We have shown that the bilayer is stable throughout the 1550-ps simulation and have demonstrated convergence of the system dimensions. Several important aspects of the bilayer structure have been investigated and compared favorably with experimental results. For example, the average positions of specific carbon atoms along the bilayer normal agree well with neutron diffraction data, and the electron density profile is in accord with x-ray diffraction results. The hydrocarbon chain deuterium order parameters agree reasonably well with NMR results for the middles of the chains, but the simulation predicts too much order at the chain ends. In spite of the deviations in the order parameters, the hydrocarbon chain packing density appears to be essentially correct, inasmuch as the area/lipid and bilayer thickness are in agreement with the most refined experimental estimates. The deuterium order parameters for the glycerol and choline groups, as well as the phosphorus chemical shift anisotropy, are in qualitative agreement with those extracted from NMR measurements.

INTRODUCTION

Fully hydrated bilayers of pure lipids have been employed as model membranes in many biophysical studies under the premise that quantitative data on the more experimentally tractable model systems provide insight into the structure and function of biological membranes. Of the several bilayer phases of hydrated phospholipids, the most biologically relevant is the L_α or "liquid crystal" phase (Small, 1986). In this phase, the hydrocarbon chains are conformationally disordered and the lipid molecules are free to diffuse in the plane of the bilayer (Pfeiffer et al., 1989). The disorder is undoubtedly important to biological function, but it has made atomic-scale structure determination impossible with present techniques.

Nonetheless, there have been many important experimental investigations of the structure of L_α phase bilayers. The main insight has been through neutron and x-ray diffraction and nuclear magnetic resonance (NMR) experiments. Neutron diffraction experiments on selectively deuterated lipids provide information on the average intramolecular configuration, namely, the mean position of a particular deuterated chemical group (e.g., CD_2) along the bilayer normal (Büldt et al., 1979; Zaccai et al., 1979). X-ray diffraction provides complementary information on the intermolecular structure, e.g., low-angle diffraction gives the lamellar spacing in samples of stacked bilayers (Levine, 1973). In addition, the profile structure may be determined by fitting a model electron density profile to the observed structure factors. The most sophisticated analysis to date is that of Zhang et al. (manuscript in preparation), where an intensity correction was used to account for stacking disorder. Deuterium NMR (DMR) yields information about the time-averaged orientation of segments in deuterated lipid molecules. The deuterium quadrupole splitting in the DMR spectrum is mainly determined by the average conformation and the amplitude of oscillations of individual segments (i.e., C-D bonds). Indeed, an order parameter, S_{CD}, defined to be proportional to the quadrupole splitting, is routinely used to characterize the behavior of the hydrocarbon chains in membranes (Seelig and Seelig, 1974). In fact, the order parameters determined from DMR measurement and the mean positions from neutron diffraction are closely related through the average intramolecular conformations (Zaccai et al., 1979). Moreover, the order parameters appear to be the best method for estimating a crucial structural quantity, the surface area per lipid in L_α phase bilayers (Nagle, 1993). This route to the area is an alternative to the traditional gravimetric method (Tardieu et al., 1973). The latter is subject to greater error because of the uncertainty in knowing how much water is between the bilayers. The number of water molecules per lipid, n_W, can be calculated reliably by combining the area deduced from the S_{CD} values with the lamellar spacing from low-angle diffraction and molecular volumes from dilatometry (Nagle, 1993).

Molecular dynamics (MD) simulations have great potential to provide an atomic-scale picture of membrane structure that complements and assists in the interpretation of experimental results. Many reports of MD simulations of phospholipid bilayers with atomic detail have appeared in the literature during the last 3 years (Damodaran et al., 1992; Venable et al., 1993; Heller et al., 1993; Stouch, 1993; Egberts et al., 1994; Huang et al., 1994; Robinson et

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al., 1994; Zhou and Schulten, 1995; Shinoda et al., 1995). Most of these studies (Damodaran et al., 1992; Venable et al., 1993; Heller et al., 1993; Stouch, 1993; Robinson et al., 1994; Zhou and Schulten, 1995) were performed at constant volume, using experimentally derived values for a crucial system parameter, the area per lipid, although there is considerable disagreement on the correct value, even for the most commonly studied phospholipid, dipalmitoylphosphatidylcholine (DPPC) (Nagle, 1993). It is difficult to assess the situation in most published constant volume simulations because the pressure is rarely reported. Pressure changes of roughly 1000 atmospheres, not uncommon in simulations of polar molecules using standard force fields, can induce phase transitions in lipid bilayers (Jonas and Jonas, 1994). Previous simulations of lipid bilayers at constant pressure in a flexible simulation cell have been based on relatively short trajectories, and convergence of the cell parameters has not been demonstrated convincingly (Egberts et al., 1994; Huang et al., 1994; Shinoda et al., 1995).

Our general goal is to show that it is possible to perform converged constant-pressure MD simulations that yield stable bilayers whose structures are in accord with established experimental results. Then we can use the results of these simulations to evaluate assumptions used in the interpretation of experimental data and, therefore, discern the best values for key structural parameters such as the area per lipid in the L_α phase. Given the sensitivity of constant-pressure simulations to the details of the potential, the first step of our approach has been to validate the potential. To this end, we have performed constant-pressure and -temperature (NPT) simulations to test the all-atom potential that we employ on a series of systems with well-known structures: solid and liquid alkanes (Tobias et al., 1995), crystals of phospholipid fragments (dilauroylglycerol, glycerylphosphorylcholine, and cyclopentylphosphorylcholine monohydrate) (Tu et al., 1995a; Tu et al., unpublished results), and a fully hydrated gel phase DPPC bilayer (Tu et al., 1995b). The important structural quantities (liquid densities, crystal lattice parameters, and bilayer area per lipid and lamellar spacing) were reproduced to within 3% in every case.

In this paper, we present the salient results of a constant NPT MD investigation of a DPPC bilayer with $n_W = 28$ water molecules/lipid at a temperature $T = 50°C$. Under these and similar conditions of hydration and temperature, the lipids are known experimentally to be arranged in a fully hydrated, L_α phase bilayer (Small, 1986). Here, we concentrate primarily on demonstrating convergence and stability in a long constant NPT simulation, and on the comparison with a variety of experimental data on the bilayer structure. We defer discussion of other aspects, such as the detailed intra- and intermolecular structure and hydration, as well as dynamical properties, to a forthcoming publication.

MATERIALS AND METHODS

The construction of the initial configuration for our constant NPT simulation involved a series of several set-up and equilibration stages. Starting with the coordinates of the two distinct molecules in the dimyristoylphosphatidylcholine (DMPC) x-ray crystal structure (Pearson and Pascher, 1979), we added two carbons to each hydrocarbon chain, used the space group operations and lattice translations of the crystal to generate a 4 × 8 monolayer of 32 DPPC molecules, adjusted the coordinates so that all of the phosphorus atoms were in the same (monolayer) plane to disrupt the crystal head group packing, and scaled the center-of-mass coordinates in the plane of the monolayer to give a surface area per lipid of 62.0 $Å^2$ to satisfy experimental data on the liquid crystal phase (Nagle, 1993). This monolayer was used as input to a 20-ps MD simulation (a timestep of 1 fs was used in all of the calculations) with periodic boundary conditions at a constant temperature of 50°C. During this simulation the positions of the phosphorus atoms were held fixed and the hydrocarbon chains became significantly disordered. A bilayer was constructed from the monolayer by using the symmetry operations of the DMPC crystal space group ($P2_1$), and adjusting the interlayer separation so that the phosphorus-phosphorus distance was 38 Å. This bilayer was subsequently subjected to 10-ps MD, again with fixed phosphorus atoms. A slab of bulk water with the same surface area as the monolayers was placed on both sides of the bilayer. The thicknesses of the slabs were chosen to give $n_W = 28$. The length of the simulation cell in the direction of the bilayer normal (i.e., the interlamellar spacing) was gradually decreased in a series of 2-ps MD simulations (with fixed phosphorus atoms) to 67.0 Å. At this point we performed a 50-ps unconstrained simulation with constant volume at 50°C. To ensure that the hydrocarbon chains were melted, we ran a series of five 20-ps simulations with constant volume at 150, 120, 90, 70, and 60°C, followed by another 100 ps at 50°C.

After constructing and equilibrating the system as described above, we performed a 1550-ps MD simulation at constant external temperature (T_{ext} = 50°C) and pressure ($P_{ext} = 0$) in a fully flexible simulation box using the hybrid algorithm developed by Martyna et al. (1994). The extended system (ES) equations of motion were integrated by using an iterative Verlet-like algorithm. The SHAKE algorithm (Ryckaert et al., 1977) was used to constrain the lengths of bonds involving hydrogen atoms. The fictitious masses of the ES variables were chosen according to the prescription given by Martyna et al. (1994), with time scales of 0.5 ps for the thermostats and 1 ps for the volume and cell variables. The Nosé-Hoover thermostat chain length was 5.

We employed the SPC/E water potential (Berendsen et al., 1987) and the all-atom lipid potential referred to in the Introduction. Periodic boundary conditions were applied in three dimensions to generate an infinite, multilamellar system, and the Ewald method was used to calculate the electrostatic interactions (Allen and Tildesley, 1989). The minimum image convention was employed to calculate the van der Waals interactions and the real-space part of the Ewald sum with simple truncation at 10 Å (Allen and Tildesley, 1989). Long-range corrections to account for the truncated van der Waals interactions were included in the energies and pressures (Allen and Tildesley, 1989). The calculation was executed in parallel/vector mode on the Cray C90 computer at the Pittsburgh Supercomputing Center using the CHARMM program (Brooks et al., 1983), version 23, as modified by us to implement the ES dynamics, minimum image periodic boundary conditions, and Ewald summation.

RESULTS AND DISCUSSION

Fig. 1 shows the time evolution of the surface area per lipid and lamellar spacing during the 1550-ps constant NPT simulation. These quantities oscillated about, but did not change appreciably from, their initial values. Thus, the bilayer was stable over the entire course of the simulation. After the extensive constant volume equilibration and 200 ps of constant NPT dynamics, the potential energy and all of the structural results presented below were converged (i.e., were oscillating about average values, but not drifting), with the exception of the phosphate chemical shift anisotropy,

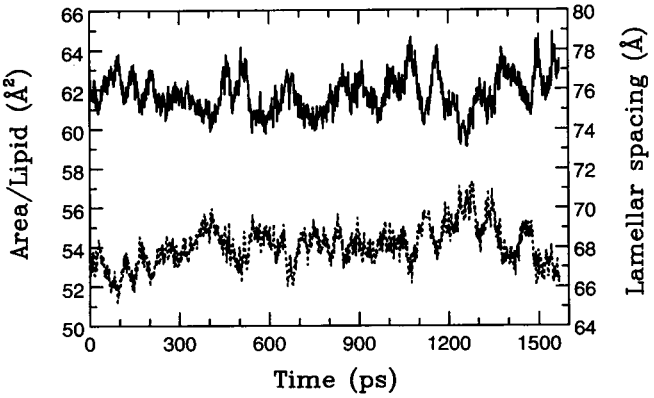

FIGURE 1 Time evolution of the area/lipid (*solid line*) and lamellar spacing (*dashed line*) during the constant NPT MD simulation of the DPPC bilayer.

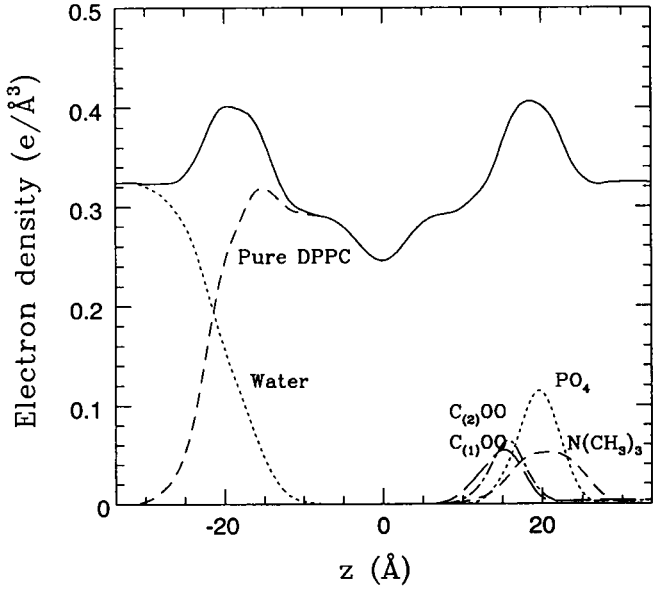

FIGURE 2 Electron density profiles along the bilayer normal, z, averaged over the simulation. The solid line is the total electron density. The broken lines on the left side of the figure show the separate contributions from the DPPC and water molecules, respectively, and on the right side the contributions from chemical moieties in the head group and acyl ester regions of the DPPC molecules.

which required 600-ps NPT dynamics to converge. Therefore, the chemical shift anisotropy reported below is an average over the last 950 ps, and all of the other results are averages over the last 1350 ps. The average area per lipid and lamellar spacing calculated over this period are 61.8 $Å^2$ and 67.3 $Å$, respectively. The latter is in good agreement with the experimentally established value of 67.0 $Å$ (Nagle and Wiener, 1988), and the former with Nagle's recent estimate of 62.0 $Å^2$ (Nagle, 1993), for fully hydrated, liquid crystal phase DPPC bilayers at 50°C.

We have computed distances from the bilayer center along the bilayer normal and compared them to results from neutron diffraction experiments to evaluate the quality of the time-averaged structure from our simulation. For the head group ammonium methyl carbon atoms Cγ, the choline methylene carbons, Cβ and Cα, and the glycerol methylene carbon atoms GC-3 (Büldt et al., 1979), the average distances we calculate from the simulation are 21.1 ± 3.0, 20.3 ± 2.6, 20.2 ± 2.4, and 17.4 ± 2.1 $Å$, respectively. The corresponding experimental values from unoriented powder L_α DPPC samples at n_W = 13.6 and 50°C are 21.8 ± 0.6, 21.2 ± 1.0, 21.0 ± 1.0, and 17.4 ± 1.5 $Å$, respectively (Büldt et al., 1979). The observation that the ammonium and choline carbon atoms have almost the same value implies that the head groups are aligned approximately parallel to the bilayer plane. From the MD trajectory we found that the average angle between the P-N vector and the bilayer plane is 17°, pointing into the water layer. The average distances from the center of the bilayer for the C4, C5, C9, C14, and C15 atoms in the hydrocarbon chains are 11.7 ± 1.7, 10.7 ± 1.8, 6.9 ± 2.0, 2.6 ± 2.0, and 1.9 ± 2.1 $Å$, respectively, from the simulation, and 12.2 ± 1.5, 10.5 ± 1.5, 8.1 ± 1.0, 3.6 ± 1.0, and 1.9 ± 1.0 $Å$, respectively, from neutron diffraction (Zaccai et al., 1979). In summary, the simulation results agree to within 1 $Å$ with the neutron diffraction results throughout the bilayer.

We have computed the electron density profile from the MD trajectory by placing a Gaussian distribution of electrons on each atomic center with a variance equal to the van der Waals radius, for each configuration, and averaging over configurations. The resulting profile, shown in Fig. 2, is nearly symmetric, as it should be for a stable bilayer at equilibrium. The peaks in the electron density correspond to the polar head groups, and the trough in the geometric center corresponds to the terminal methyl region of the hydrocarbon chains in the center of the bilayer. The regions between the peaks and the trough are the methylene groups, and the narrow regions at the outer edges of each profile are the water layers between adjacent bilayers. The distance between the two head group peaks, 38.2 $Å$, is in the range of values, 39.6 and 36.4 $Å$, read from electron density profiles obtained by Fourier reconstruction and hybrid model fits, respectively, of intensity corrected low-angle diffraction data (Zhang et al., manuscript in preparation). The right side of the figure shows the electron density contributions from the polar region, i.e., the phosphate, ammonium, and the two acyl ester groups. The position of the phosphate group (PO_4) is at the outer side of the electron density profile peak position, and the distance between the phosphate groups is 39.8 $Å$. The left side of the figure shows the separate contributions from the pure DPPC bilayer and the water molecules. As in the gel phase (Tu et al., 1995b), the peak in the DPPC contribution coincides with the glycerol ester groups rather than at the high electron density phosphate group. In contrast to the situation in the gel, the acyl ester regions are well hydrated in the liquid crystalline bilayer.

Next we compare the hydrocarbon chain behavior in the simulation with that reflected by the deuterium order parameters and phosphate chemical shift anisotropy from

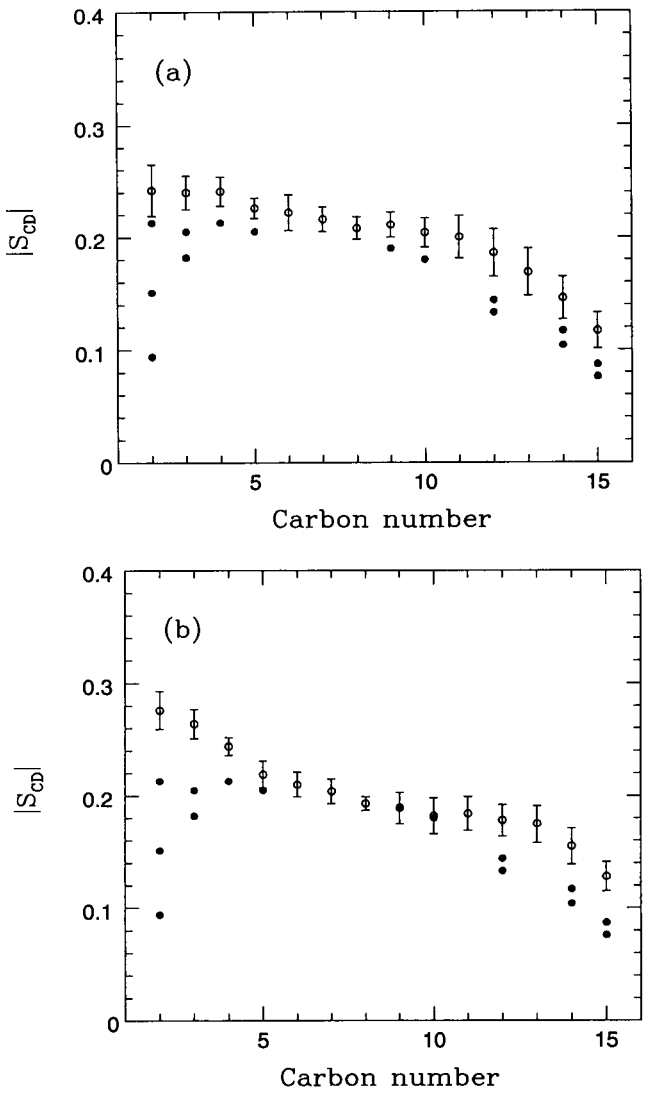

FIGURE 3 Comparison of simulation (*open circles*) and experimental (*filled circles*) hydrocarbon chain deuterium order parameters. The MD results for the *sn*-1 chain are shown in *a*, and the *sn*-2 chain in *b*. The experimental results (Seelig and Seelig, 1974) have not been assigned to particular chains except at carbon 2, where the largest value is for the *sn*-1 chain and the two lower values are for the *sn*-2 chain (Seelig and Seelig, 1975). The error bars on all of the reported simulation results represent $\pm\sigma$, where σ is the standard deviation of averages computed over blocks of 100 ps.

NMR experiments. Fig. 3 compares the hydrocarbon chain deuterium order parameters calculated from the MD trajectory, plotted separately for the two chains in Fig. 3, *a* and *b*, with those from DMR on DPPC at 50°C (Seelig and Seelig, 1974). The plateau values, $S_{CD} \approx 0.2$, in the middles of the chains (carbons 5 through 10), are reproduced reasonably well by the simulation. However, the simulation predicts too much order at the two ends of each chain. The most significant deviation is that the simulation reverses the relative magnitude of the order parameter for carbon 2 in the two chains (Seelig and Seelig, 1975). The differences between the calculated and experimental order parameters are difficult to explain, and could be due to subtle deficiencies in the hydrocarbon chain potential, or incomplete sampling of the chain conformations and/or long time-scale lipid "wobble" motions (Pastor et al., 1988). We analyzed the chain conformations and found that there are 14, 25, 18, 23, 20, 20, 20, 23, 23, 25, 26, and 32% *gauche* defects in the last 12 bonds (C3-C4, ... , C14-C15), respectively. Thus, the average fraction *gauche* in the simulation, 0.22, is significantly lower than the value 0.31 estimated by using a statistical mechanical analysis of the experimental order parameters (Schindler and Seelig, 1975).

Finally, we compare the simulation results to available NMR data on the order in the glycerol and head group regions. The deuterium order parameters calculated from the simulation for the choline methylene and methyl groups are small, ranging from 0.001 to 0.024, and are consistent with the small quadrupole couplings (1–6 kHz) measured by Gally et al. (1975). For the methylene group at the glycerol/phosphate connection (GC-3), we found $S_{CD} = 0.23 \pm 0.02$, which agrees well with the value 0.22 extracted from DMR experiments by Gally et al. (1975). The phosphorus chemical shift anisotropy, σ_a, calculated from the simulation at 50°C, -43 ± 3 ppm, is slightly high compared to the values -49 ppm at 44°C and -44 ppm at 59°C measured by Niederberger and Seelig (1976). Using the ^{31}P chemical shift tensor measured by Kohler and Klein (1976), the chemical shift anisotropy can be expressed as $\sigma_a = -56S_{11} + 133S_{33}$ ppm, where S_{11} (S_{33}) is the order parameter for the vector connecting the esterified (nonesterified) oxygens of the phosphate group (Niederberger and Seelig, 1976). The average values of S_{11} and S_{33} calculated from the simulation are 0.08 ± 0.03 and -0.29 ± 0.02, respectively. The fact that the simulation result for σ_a is a little high means that the calculated value of S_{11} is a little low and/or S_{33} is a little high.

CONCLUSIONS

In conclusion, we have carried out a constant-pressure and -temperature MD simulation of a fully hydrated DPPC bilayer in the L_α phase at 50° for more than 1.5 ns. We have shown that the bilayer is stable throughout the simulation and have demonstrated convergence of the system dimensions. Several important aspects of the bilayer structure have been investigated and compared favorably with experimental results. For example, the average positions of specific carbon atoms along the bilayer normal agree well with neutron diffraction data, and the electron density profile is in accord with x-ray diffraction results. The hydrocarbon chain deuterium order parameters agree reasonably well with NMR results for the middles of the chains, but the simulation predicts too much order at the chain ends. In spite of the deviations in the chain order parameters, the hydrocarbon chain packing density appears to be essentially correct because the area per lipid and bilayer thickness are in agreement with the most refined experimental estimates.

The deuterium order parameters for the glycerol and choline groups, as well as the phosphorus chemical shift anisotropy, are in qualitative agreement with those extracted from NMR measurements. The results of our simulation should prove useful in validating or refining models used in the interpretation of experimental data. Indeed, the present results confirm the methods used to estimate the values of the surface area and the number of water molecules per lipid used to initiate our simulation.

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