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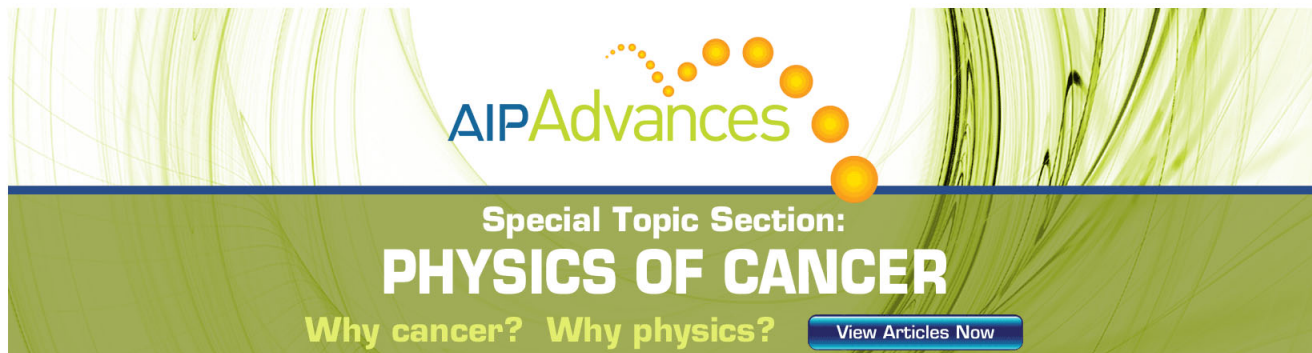
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Hydration strongly affects the molecular and electronic structure of membrane phospholipids

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We investigate the structure and electronic properties of phosphatidylcholine (PC) under different degrees of hydration at the single-molecule and monolayer type level by linear scaling *ab initio* calculations. Upon hydration, the phospholipid undergoes drastic long-range conformational rearrangements which lead to a sickle-like ground-state shape. The structural unit of the tilted gel-phase PC appears to be a water-bridged PC dimer. We find that hydration dramatically alters the surface potential, dipole and quadrupole moments of the lipids and consequently guides the interactions of the lipids with other molecules and the communication between cells. © 2012 American Institute of Physics. [<http://dx.doi.org/10.1063/1.3694280>]

I. INTRODUCTION

Phospholipid membranes are essential functional and structural components of cells that are involved in numerous cellular physico-chemical processes occurring within the cells or between them. Despite the apparent importance of membrane electrostatic behavior for the functioning of membranes, insights into the electronic structure of the phospholipid membrane are scarce. Specifically, the magnitude, the orientation, and the origin of the dipole potential remain amongst the least understood aspects of the biological membrane;¹ the differences in the reported values are considerable and are of the same order of magnitude as the potential itself. The detailed distribution of charge density, dipole and quadrupole moments of membrane phospholipids and, in particular, the influence of the interfacial water molecules on the electric potential at the interface have not been investigated. Indeed these problems are difficult to address because of the complexity of the membrane system.²

Hydrated phospholipids are also difficult subjects for structural investigations. The structure of the benchmark lipid dipalmitoyl phosphatidylcholine (DPPC) has been studied with x-ray diffraction but with limited success.³ The main obstacle in resolving the structure are fluctuations that leads to smearing of the Bragg peaks.⁴ NMR, ESR, and optical spectroscopic techniques have been applied to gain structural insight into hydrated DPPC as well, but the reported structural parameters of the phospholipids have significant uncertainties and the structural organization of the interfacial water layer has remained challenging to resolve.^{5,6} Each technique has its own drawbacks: NMR spectroscopy of DPPC vesicles and the bilayer has turned out to be challenging due to broad spectral

linewidths and quadrupolar splitting;⁷ optical spectroscopy is helpful, but since it is indirect, it needs consistent input from theory.

Classical simulations have proven useful in studying these experimentally difficult systems and in providing a quantitative basis for our understanding of lipid membranes. Nevertheless, classical simulations are affected by imperfections of the force field.⁸ *Ab initio* calculations are, in principle, able to address these challenges.⁹ However, due to the inherently large system size, first principle treatments were not feasible to this date, given the non-linear scaling of the computational effort with system size. Just recently, the linear scaling version of density functional theory (DFT) with localized Wannier-like wave functions has been developed which makes such calculations feasible.^{10,11} This algorithm is based on the concept of locality and uses a modified energy functional which avoids direct wave function orthogonalization. For a system composed of n atoms, the computational complexity reduces from $O(n^3)$ to nearly $O(n^1)$.^{11,12}

Here, we investigate the structure of DPPC under different degrees of hydration using this newly developed approach to density functional theory¹² (see method SM1 of supplementary material for details of the calculation).²⁷ Briefly, we used Troullier-Martins type pseudopotentials along with double- ζ singly polarized basis set as implemented in density functional code SIESTA.¹² We used local density approximation as the exchange-correlation energy functional, with Ceperley-Alder parametrization. By performing a large scale calculation, we explore the influence of neighboring DPPC molecules (by applying the periodic boundary condition, i.e., monolayer type structure) on the structure of the hydrated lipid. We also examine the molecular interplay between the lipid and the interfacial water layer and investigate the structural features of the water interfacing the lipid. By comparing the obtained structure with the existing

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experimental data, the structural findings are validated. Our results confirm previous x-ray diffraction studies suggesting that the super lattice unit cell of DPPC contains two lipid molecules.¹³ Next, we study the electrical properties of hydrated DPPC and hydrated DPPC monolayer type to gain insight into the structure-function relationship. Finally, we perform a similar study on the structure and electrical properties of phosphatidyl ethanolamine, the second most abundant phospholipid in cell membranes.

II. RESULTS AND DISCUSSION

We find that upon hydration, DPPC undergoes a dramatic long-range conformational change (Figs. 1(a) and 1(b) and Table S1 of supplementary material). With 50 water molecules,^{14,15} the head group of the lipid and the proximal tail region are fully covered. The glycerol plane rotates and assumes a parallel orientation with respect to the plane of the tails and the glycerol backbone lines up with the sn_1 chain with an angle of 171.4° . The sp^2 planes of sn_1 and sn_2 carbonyls make an angle of about 23.8° , and the carbonyl groups take an anti-parallel orientation (Table S2 of supplementary material).²⁷ These conformational rearrangements lead to a change in the compaction of the structure (Table S1).²⁷ When we increased the number of water molecules to 75, the confor-

mation of the lipid remained nearly the same. DPPC has been commonly referred to as a cylindrical molecule.¹⁶ We find that the ground-state shape (at zero temperature) of the hydrated DPPC differs from a cylindrical geometry and adopts a sickle-like overall shape (Fig. 1(b)) with tail bending angles of about 24° and 14° relative to the molecular axis of unhydrated DPPC. With other choices for exchange-correlation functionals including local spin density approximation, generalized gradient approximation, and van der Waals functionals we observed only minor differences.

This conformational rearrangement is favored because it allows water chains to bridge the oxygen atoms of the lipid. We estimated water-lipid interaction energy to be ~ -0.20 eV (-19.30 kJ/mol) for DPPC system with 50 waters and 11 water-lipid H-bonds (see method SM2 of supplementary material).²⁷ This is estimated by separating the water cluster from the lipid part and comparing the energy of the two parts with the energy of the system. Thus, the energy difference also includes the interaction energy of the water cluster with the electric field of the lipid. To further understand the mechanistic basis underpinning the conformational changes, we removed 30 water molecules and calculated the structure of DPPC with 20 water molecules, which suffices to hydrate the hydrophilic parts of the lipid head and building the water bridges. Indeed, the phosphate and ester group oxygens form hydrogen bonds similar to what we find with full hydration and the water chains connecting the groups emerge. With partial hydration, we found a similar conformational rearrangement and overall shape change in the lipid.

We also studied the structure of two neighboring DPPC molecules (2DPPC) with associated water molecules ($N_{H_2O} = 64$) with periodic boundary conditions. We observe that two DPPC molecules adopt an orientation in which the dipole moments are in a nearly anti-parallel arrangement and the two tail planes face each other (Figs. 1(b) and 1(c)). In this arrangement, the tail plane of one of the lipids convexes towards the other one. Our result is in agreement with previously reported experimental evidence for long-range cooperative distortion of lipid tails.¹⁷ In a minimum energy configuration, units of 2DPPC are expected to pack in such a way that the dipole-dipole interactions are most favorable (Fig. 1(c)). The area per lipid, is found to be 46 \AA^2 . For the hydrated DPPC membrane, this value is in agreement with experimentally measured values in tilted gel phase as well as classical simulations of the system.^{18,19}

We then investigated the nature of intermolecular interaction in hydrated 2DPPC. We observed that two water bridges connect sn_2 carbonyls of the two DPPCs (Fig. 1(b)), in accordance with previous studies.²⁰ The carbonyl groups and the two water bridges adopt a nearly planar geometry. The hydrated 2DPPC complex is stabilized by dipole-dipole interaction, water bridges and van der Waals interaction of the tails. We therefore propose the 2DPPC complex as the structural unit of the DPPC membrane. This is in agreement with previous studies²¹ including x-ray diffraction studies where the reported super lattice unit cell of DPPC contains two lipid molecules.¹³ We estimated the contribution of the water bridges to the stability of hydrated 2DPPC complex. We find that the removal of the bridges destabilizes the system

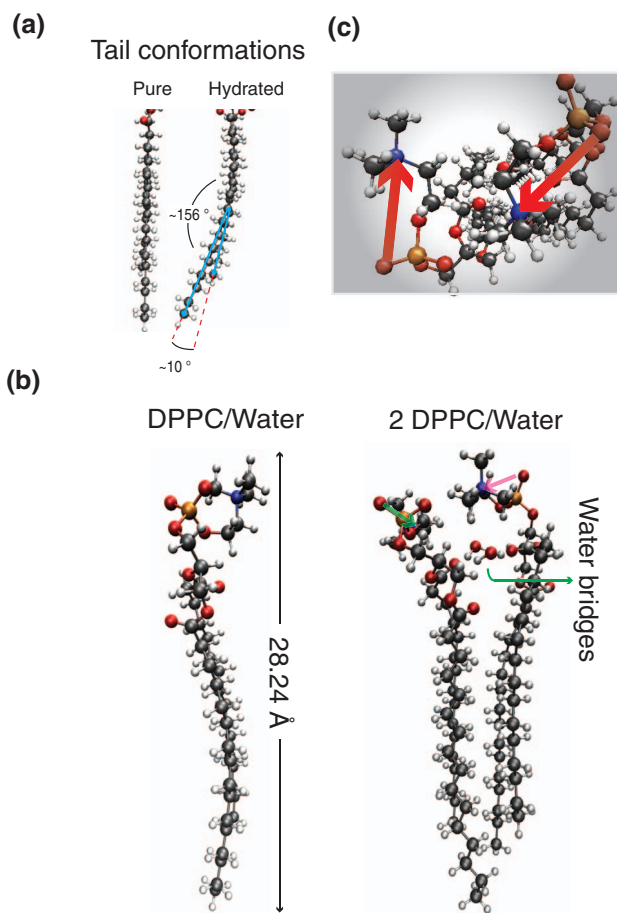


FIG. 1. (a) and (b) display the minimum energy configurations of DPPC, hydrated DPPC, and 2DPPC. Water molecules are not displayed in order to visualize the lipid conformations. (c) Two anti-parallel lipids are proposed as structural unit in DPPC membrane. 2DPPC system was simulated under periodic boundary condition. The area per lipid is calculated to be 46 \AA^2 .

by ~ 2.05 eV (197.79 kJ/mol) per water bridge (see method SM2).²⁷

Next, we address the relation between the structure and the electrical properties of the lipids in monolayer type structure. We compute the electrical properties of non-hydrated DPPC at its minimum energy configuration. Not surprisingly the head group carries a high charge density in the vicinity of phosphate oxygen and quaternary nitrogen. However, the centres of positive and negative charges do not coincide perfectly with the P and N atoms. The direction of the electric dipole \mathbf{P} is about $\Phi = 56.51^\circ$ and $\Theta = 18.34^\circ$ (from the plane of the head) while the $\text{PO}^- - \text{N}^+$ vector has $\Phi = 65.69^\circ$ and $\Theta = 18.66^\circ$. The electric dipole of DPPC is calculated to be 10.30 D. Thus, the dipole moment of DPPC is almost 5 times larger than that of a water molecule ($\sim 1.85\text{--}2.6$ D).²⁶ The $\text{PO}^- - \text{N}^+$ dipole is around 21.30 D ($d \sim 4.43$ Å). It seems that the absolute value of charges around the atoms N and PO^- are distributed in the space and give smaller charge concentration around these atoms. We also find that single DPPC has an electric quadrupole moment. We calculated the quadrupole tensor for the single DPPC with respect to the center of mass of lipid (see Table S3). The magnetic dipole moment was negligible. The calculated charge density (Figs. 2(a) and 2(b)) shows excellent agreement with the electron density profile from x-ray studies.^{4,22} Figure 2(c) presents the electric potential profile of DPPC with calculated equipotential lines. Electronic density of states of the system is given in Fig. S1.²⁷

The presence of water leads to a conformational change in the entire molecule and is therefore also expected to affect the electric moments. Indeed, the $\text{PO}^- - \text{N}^+$ distance reduces by nearly 0.9 Å to 3.558 Å in hydrated DPPC with 20 water molecules. The conformational change induced by the anisotropic hydration causes an increase ($>80\%$) in the dipole moment of the full system to 18.42 D. As the number of water molecules is increased from 20 to 50, the dipole moment reduces to 9.87 D due to cancellation of the dipole moments of the isotropically oriented molecules (Fig. 2(e)). For DPPC with 75 water molecules, we find a dipole moment of about 10.42 D. The calculated dipole moment is in agreement with experimental reports.^{23,24} For 2DPPC with 64 water molecules, we found a net electric dipole of about 0.4798 D. It is noteworthy that the distribution of charge density is more diffuse in hydrated DPPC as compared to pure DPPC, which means higher order electric moments become significant (Table S3 of supplementary material).²⁷ This implies that hydrated DPPC interacts with the electric field gradient in its environment and influences its interaction with ions. Figure 3 displays the surface potential of a DPPC monolayer type structure. The total electrostatic potential (surface potential) is defined as the sum of the Hartree potential plus the local pseudopotential, at the mesh points, which are used to calculate the real-space quantities (e.g., charge density). The surface potential fluctuates between positive and negative values along the normal to the lipid surface and within the surface with 0.5 nm spacing. Therefore, a sensor scanning the surface or approaching the surface along the normal, will sense positive or negative potential values depending on its position. This spatial fluctuation of the potential may account for

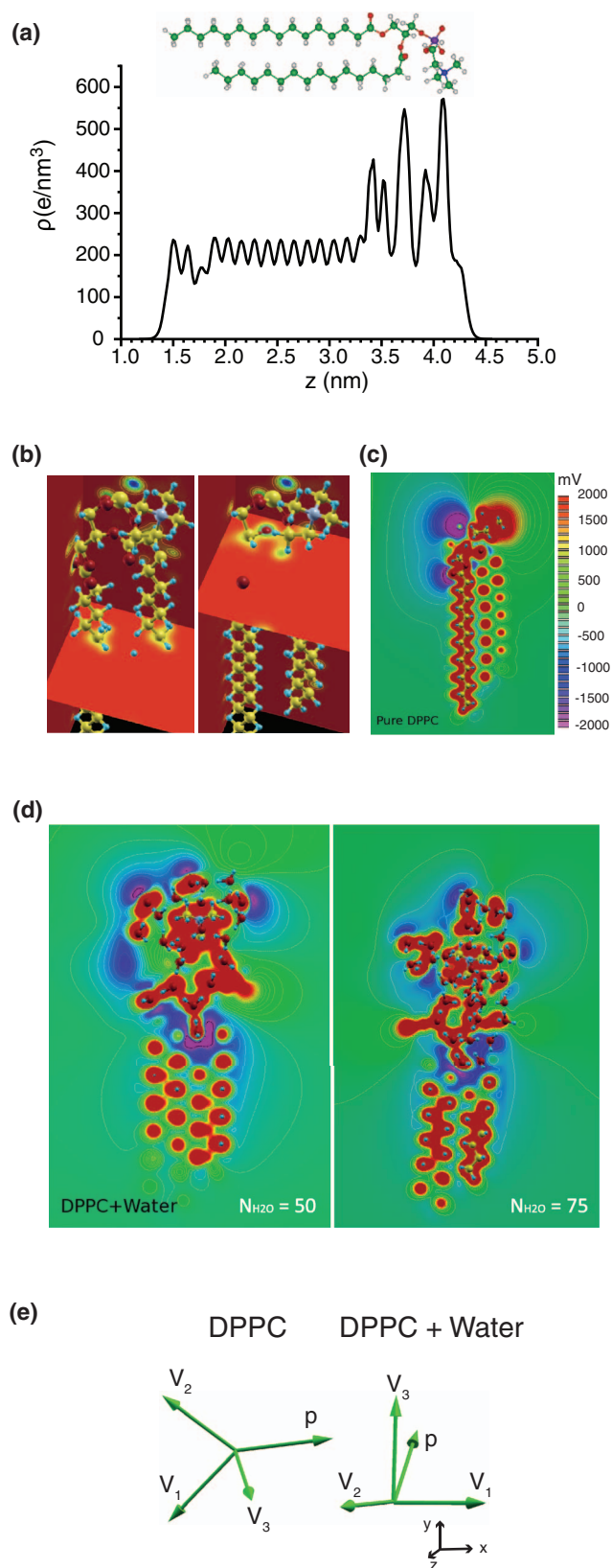


FIG. 2. Electronic properties of hydrated DPPC molecule. (a) and (b) show electron density profile along the long axis of lipid. Charge density is averaged for a disc with negligible thickness (0.078 Å). In (c) and (d), the calculated surface potentials are presented by equipotential lines for DPPC with $N_{\text{H}_2\text{O}} = 0, 50, 70$. The color coding scheme is the same in all panels. (e) Electric dipole (\mathbf{p}) and quadrupole moments (\mathbf{V}) are illustrated for DPPC and hydrated DPPC ($N_{\text{H}_2\text{O}} = 50$). y -axis coincides with the long axis of the lipid and the x -axis lies within the plane of the tails of the unhydrated lipid.

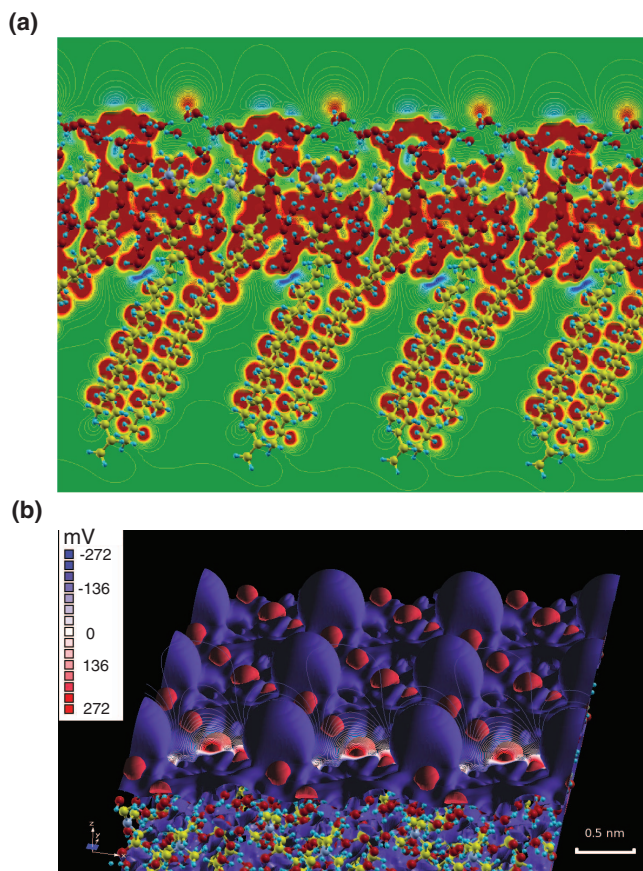


FIG. 3. (a) Tilted gel-phase type structure of relaxed hydrated 2DPPC with 32 water molecules per lipid. The tilt angle is about 28° . The color coding scheme is the same in Fig. 2(c). (b) The calculated surface potential of this monolayer type structure.

some of the seemingly contradictory experimental reports on the membrane surface potential.¹

Finally, our study can be extended to other lipids that together with PC define the electrical properties of cellular membranes (Fig. S2 of supplementary material).²⁷

III. CONCLUSION

In summary, we calculated the ground state conformation, electric moments, and surface potential of phospholipids under various degrees of hydration and showed how the interfacial water layer determines the shape and electrical properties of the molecule and mediates inter-lipid interactions. We note that due to the large number of degrees of freedom available for these complex systems, reaching the global energy minimum configuration is often difficult. For the structures presented in this study, we find that all atoms are indeed positioned in their local energy minima which is evidenced by the fact that the eigenfrequencies for the phonon modes of the system are all positive real numbers. Our study invites for future quantum molecular dynamics simulations at body temperature which will be able to provide an ensemble of structures available for the system and to show the fluctuations in the magnitude of the dipole moments and the structural parameters.

The relevance of this study lies upon the fact that the electric moments and surface potential influence the geometry,

phase behavior, and mechanics of lipid membrane and govern the interaction of the membrane lipids with dynamically associated proteins and RNA molecules.²⁵

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²⁷See supplementary material at <http://dx.doi.org/10.1063/1.3694280> for the structural parameters (Table S1, S2), eDOS (Fig. S1, Table S4), electric quadrupoles (Table S3), and the details of calculations (methods SM1, SM2).