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Water Permeation Through DMPC Lipid Bilayers using Polarizable Charge Equilibration Force Fields

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Abstract

We investigate permeation energetics of water entering a model dimyristoylphosphatidylcholine (DMPC) bilayer via molecular dynamics simulations using polarizable Charge Equilibration (CHEQ) models. Potentials of mean force show 4.5–5.5 kcal/mol barriers for water permeation into bilayers. Barriers are highest when water coordination within the bilayer is prevented, and also when using force fields that accurately reproduce experimental alkane hydration free energies. The magnitude of the average water dipole moment decreases from 2.6 Debye (in bulk) to 1.88 Debye (in membrane interior). This variation correlates with the change in a water molecule's coordination number.

Keywords

LIPID BILAYER; DMPC; WATER; TIP4P-FQ; CHARGE EQUILIBRATION; POLARIZABILITY; FORCEFIELDS

I. INTRODUCTION

Lipid bilayers represent an important constituent of physiological membranes. They provide a supporting environment for the transmembrane proteins which comprise approximately one-third of the human genome and contribute to the regulation of small molecule diffusion through biological membranes.¹ From a physicochemical perspective, interactions of phospholipid bilayers with water are particularly interesting. Hydrophobic effects between water and the lipid tails drive the formation of bilayers such that the water is free to interact with the hydrophilic head groups while minimizing exposure to the hydrophobic tails. Despite the relatively unfavorable water-lipid interaction, water has been found to permeate into the hydrophobic core and assist the transport of ions and small molecules across these membranes.^{1–5}

Experimental studies utilizing scattering techniques (neutron, X-ray) and spectroscopy (NMR, fluorescence, infrared, vibrational sum frequency generation) have explored hydration effects in membranes.^{1,6–9} Computer simulations have also been employed to complement experimental studies with an atomically/molecularly resolved view of the structure and dynamics of lipid bilayers.^{3,10–13} The field of molecular simulations of model

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bilayer systems and integral membrane proteins in model bilayers using current state-of-the-art fixed-charge (additive) force fields is mature.

The energetics of small molecule permeation across lipid membranes is actively studied using a variety of coarse-grain and all-atom molecular simulations.^{5,14–16} MacCallum et al.⁵ examined the free energy for transporting amino acid residues from bulk water to the interior of the DOPC lipid bilayer. For polar and charged residues, they observed water following the amino acids into the center of the lipid bilayer. In the case of the polar aspartate (ASP) residue, water defects persisted at ASP-bilayer center distances of 4 Å, but dissipated at distances of 3 Å where favorable hydration of the residue was outweighed by the free energy penalty of defect formation. Orsi et al.¹⁵, while considering the permeability of water and small molecules with different functionalities across DMPC bilayers, observed the intrusion of water molecules and head group atoms into the lipid region following polar molecules (acetamide, acetic acid, methanol) into the bilayer. Conversely, nonpolar solutes were not shown to significantly perturb the bilayer, leading to the general conclusion that these distortion effects were related to the degree of polarity of the permeant molecule.¹⁵

Recent simulations of the DMPC bilayer using polarizable Charge Equilibration (CHEQ) force fields demonstrated a reduced free-energy barrier of ~ 5 kcal/mol for transfer of a water molecule from bulk to the lipid interior.¹¹ This value is approximately 1 kcal/mol less than results from simulations using non-polarizable force fields. This resulted in enhanced penetration of the polarizable TIP4P-FQ water molecules into the lipid tail region. However, the CHEQ 3 hexane force field from which the DMPC lipid tails were parameterized predicted a solvation free energy that was too favorable (1.80 ± 0.5 kcal/mol compared to the experimental value of 2.550 kcal/mol). Recent modification to the CHEQ alkane force field improved the agreement in hexane hydration free energy (now 2.50 ± 0.20 kcal/mol) with experiment.¹⁷ It is anticipated that this reparameterization will reduce the extent to which water is able to enter the interior of a phospholipid bilayer. Furthermore, based on previous observations of defects following permeant polar molecules such as water, one can question the role solvent coordination plays in the permeation of water into these bilayers. That is, how does the energetic penalty for permeation of a water molecule change when it is unable to maintain its coordination with other water molecules?

In this contribution, we investigate water permeation into the lipid interior of a model DMPC bilayer using all-atom molecular dynamics (MD) simulations and CHEQ force fields. We compare the potential of mean force (PMF) for transfer of an isolated water molecule into the lipid interior versus water which is free to remain partially hydrated via the formation of defects. Furthermore, we examine the influence of the reparameterized alkane region and the coordination of a water molecule on its permeation into this hydrophobic region. Such a study is timely and in the spirit of force field refinement which continues to be of interest to the molecular modeling community.^{18,19}

II. METHODS

We performed all-atom molecular dynamics simulations of 72 DMPC molecules (36 molecules per leaflet) and 2836 water molecules in the constant pressure, surface area, and temperature (NP_AT) ensemble. We consider three fully-polarizable DMPC-water systems: (1.) the original force field employed in a previous study by Davis et al. (CHEQ Orig),¹¹ (2.) the CHEQ force field with a planar restraint to prevent water from entering the lipid region of the bilayer (CHEQ Planar), (3.) a modified CHEQ force field using alkane-water interaction parameters that were refined to improve the free energy of hydration for alkanes (CHEQ New Par).¹⁷ In all systems, water is represented by the TIP4P-FQ model.²⁰ We refer readers to references^{11,17,20} (and references therein) for a detailed discussion of the CHEQ

formalism and models used in this work. Dynamics were propagated with a Verlet leapfrog integrator with a 0.5 fs timestep. The simulation cell had fixed lateral dimensions ($L = L_x = L_y = 46.8 \text{ \AA}$); the z -dimension (normal to the DMPC-water interface) was free to fluctuate. These lateral dimensions correspond to a surface area per lipid of $60.84 \text{ \AA}^2$, which is within the uncertainty of the experimental value, $\langle SA \rangle = 60.6 \pm 0.5 \text{ \AA}^2$.²¹ Constant pressure was maintained at 1 atm in the z -dimension using the Langevin piston method with a piston mass of 750 amu. System temperature was maintained at $T = 303 \text{ K}$ using a Nosé-Hoover thermostat.²² Particle Mesh Ewald²³ was implemented to treat conditionally convergent long-range electrostatic interactions; $1 \text{ \AA}$ spacing was used for the fast Fourier transform grid and the electrostatic screening parameter was set to $\kappa = 0.320$. For each system, a single water molecule was constrained at a given position relative to the center of mass of the lipid bilayer. For the umbrella sampling, water-lipid interior distances of $0\text{--}30 \text{ \AA}$ were sampled in $1 \text{ \AA}$ increments resulting in 31 windows. Force constants were chosen in the range $k = 1\text{--}2 \text{ (kcal/mol)/\AA}^2$ such that there was sufficient overlap in sampling between adjacent windows without significant drift from target distances. Each window was sampled for at least 3 ns, totaling over 90 ns per system. PMFs were calculated from the biased simulation data using the Weighted Histogram Analysis Method (WHAM).²⁴

III. RESULTS AND DISCUSSION

Number density profiles for various components of each system are shown in Figure 1. In particular, we show the density of head group atoms (nitrogen, phosphorous, oxygens) and water. Water density approaches zero at different positions. Transitioning from bulk water to the lipid interior, CHEQ Planar demonstrates the earliest and most rapid decrease in water density; this decrease at $z \approx 12 \text{ \AA}$ corresponds to the position of the constraint preventing water from entering the lipid tail region. The CHEQ Orig and CHEQ Newpar systems demonstrate similar water behavior, although the water density is slightly reduced for CHEQ Newpar. This is consistent with the less favorable alkane-water interaction in the CHEQ Newpar force field.

The density maxima associated with head group atoms are sharper in the case of the CHEQ Planar system than the other systems. Based on Gaussian fits, the variance in the phosphorous density in the CHEQ Planar system is 53 – 60% of the variance of CHEQ Orig and CHEQ Newpar. Restricting water (other than the target molecule) from entering the lipid region reduces the extent of spatial fluctuations of head groups normal to the DMPC/water interface. This is expected since the formation of water defects (which have been shown to pull head group atoms into the lipid region¹⁵) is prevented.

We study the energetics of water permeation by calculation of potentials of mean force (PMF) for each system. Initially, we consider PMFs calculated using umbrella sampling and WHAM²⁴. The PMFs are shown in Figure 2 and the energetic barriers for water permeation into the bilayer center are summarized in the Table I. We focus our discussion on the comparison of the PMF for the CHEQ Orig parameterization with the CHEQ Planar and the CHEQ Newpar systems. Comparison with the former allows us to assess the energetic change associated with restricting the target water molecule from pulling additional water molecules into the lipid interior. Using WHAM, we calculate the potential of mean force to be 4.46 kcal/mol for CHEQ Orig and 5.21 kcal/mol for CHEQ Planar. Qualitatively, CHEQ Planar demonstrates a sharper barrier approaching the bilayer interior than CHEQ Orig. Limiting the extent to which the water molecule of interest remains hydrated within the lipid region reduces the favorability of populating positions where $z < 12 \text{ \AA}$. As discussed below, the difference in these PMFs is largely due to differences from the water contribution.

The second comparison suggests the influence of the new alkane parameterization on the energetics of water penetration into the bilayer. The reparameterization of interactions between small-chain alkanes and water¹⁷ yields alkane hydration free energies that are less favorable than those calculated using CHEQ Orig.¹¹ In the case of hexane, the reparameterization results in $\Delta G_{\text{hydration}} = 2.5 \pm 0.2$ kcal/mol (compared to the experimental value of $\Delta G_{\text{hydration}} = 2.550$ kcal/mol); this is approximately 0.7 ± 0.5 kcal/mol higher than the original parameterization. Not surprisingly, the revised parameterization predicts a PMF barrier nearly 0.8 kcal/mol larger than the original parameterization. Qualitatively, an enhancement is expected from the less favorable interaction between water and the alkane.

The PMF calculated in this study for the original parameterization (CHEQ Orig) is approximately 0.5 kcal/mol more favorable than previously reported by Davis et al.¹¹ In that study, however, the PMF for water penetration into the center of the bilayer was determined from the water density profiles as

$$\Delta G = -RT \ln \frac{\rho(z)}{\rho_{\text{bulk}}} \quad (1)$$

This approach provides a reasonable estimate of the free energy difference between water in bulk and lipid interior, but does not thoroughly sample highly energetic regions. As a further analysis, we compute PMFs directly from the water density profiles using Eq. 1; these PMFs are compared to those computed with WHAM in Figures 2b–d. For this analysis, the water density profiles were calculated using only windows where water was constrained 25 – 30 Å from the center of the bilayer. The inclusion of windows below these would bias the water density at lower z positions; consequently, this would artificially reduce the free energy barrier for water molecules entering the lipid bilayer as calculated using this method. In the case of the CHEQ Orig simulations, the PMF determined from the water density is approximately 5 kcal/mol, in agreement with the previously reported value.¹¹ Although the PMF as calculated using WHAM and the unbiased water density profiles differ by ~ 0.5 kcal/mol, some discrepancy is expected due to the difficulty in sampling water in the lipidic interior without imposing constraints. We compare PMFs calculated using these different approaches for CHEQ Planar and the CHEQ Newpar in Figures 2b and d, respectively. In the case of CHEQ Planar, no water molecules can access the bilayer below $|z| \approx 12$ Å resulting in an infinite PMF in the range $z = -12$ to 12 Å. CHEQ Newpar also exhibits a 5 kcal/mol PMF from bulk water to the center of the bilayer. Unlike CHEQ Orig, the PMF computed from the water density profile is reduced at $z = 0$ relative to the slightly higher z values ($z = 3$ –5 Å) in qualitative agreement with PMFs calculated using fixed charge force fields.^{3,11} This local minimum in the PMF coincides with a local maximum in the profile of fractional free volume available for water (Figure 2). We calculate fractional free volume using the approach of Marrink et al.^{12,25} Grid spacing of ~ 0.2 Å is employed in order to capture subtle features in this profile. Similar to the results for model DPPC bilayers with the CHEQ force field¹², we observe plateaus in this profile.

We next consider the individual contributions from the DMPC bilayer and neighboring water molecules to the PMF. We calculate the PMF as

$$\Delta W = - \int_{\xi=30}^{\xi=0} \langle F_z(\xi) \rangle d\xi \quad (2)$$

where ζ is the distance the target molecule was constrained from the DMPC center of mass and $\langle F_z(\zeta) \rangle$ is the average force in the direction normal to the water-DMPC interface as experienced by the target water molecule when constrained to position ζ . The bounds of integration are from bulk water ($\zeta = 30 \text{ \AA}$) to the center of the bilayer ($\zeta = 0 \text{ \AA}$). This approach for calculating the PMF allows for the decomposition into contributions from water and DMPC as:

$$\Delta W = \Delta W_{\text{DMPC}} + \Delta W_{\text{water}} = - \int_{\zeta=30}^{\zeta=0} \langle F_{z,\text{DMPC}}(\zeta) \rangle d\zeta - \int_{\zeta=30}^{\zeta=0} \langle F_{z,\text{water}}(\zeta) \rangle d\zeta. \quad (3)$$

Results of this decomposition are shown in Figure 3; numerical results are given in Table I. All results from this decomposition are expressed relative to the PMF in bulk water ($z = 30 \text{ \AA}$). The total PMF calculated using this method is in good agreement with the results determined using WHAM (matching both the qualitative PMF profile and the magnitude of the difference between bulk water and bilayer interior). In the lipid interior ($z = 0 - 5 \text{ \AA}$), DMPC has a strong positive contribution to the PMF. The positive contribution is largest in the CHEQ Newpar system, which is expected since the alkyl region for this model has a less favorable hydration free energy. The DMPC contribution is essentially the same for the CHEQ Planar and CHEQ Orig systems due to use of the same parameters for modeling the lipid tails. The contributions from water are negative in the lipid region with the planar system showing the least negative contribution. Interesting observations can also be made traversing from bulk water into the bilayer. Near $z = 22 \text{ \AA}$, the DMPC contribution shows a minimum of approximately 1.5 kcal/mol. This minimum occurs at the onset of headgroup density, suggesting a favorable interaction between the headgroup and water. However, this minimum is essentially offset by a barrier in the water contribution which suggests the penalty for water molecules to leave the bulk region. At distances closer to the bilayer center of mass, the contributions from water become more favorable whereas those from DMPC become largely unfavorable. The features of the contributions to the PMFs are qualitatively similar for all models, except in the case of the water contribution for CHEQ Planar. Here, a pronounced minimum occurs at $z = 16 - 17 \text{ \AA}$, which is likely the result of an increased water density in this region compared to the CHEQ Orig and CHEQ Newpar systems.

The PMF barriers computed in this work (4.5 – 5.5 kcal/mol) are consistent with values from other computational studies. Using a multiscale atomic level-coarse grain model, Orsi et al. calculated a transfer free energy of 6.7 kcal/mol for water from bulk to bilayer center.¹⁵ Sugii et al. used the united-atom DMPC representation of Smondyrev and Berkowitz in conjunction with the TIP3P water model to predict a transfer free energy of approximately 5.4 kcal/mol.²⁶ Using a cavity insertion approach, Jedlovsky and Mezei calculated a free energy barrier of 13 kcal/mol for inserting a water molecule into the interior of a lipid bilayer.²⁷ In all systems examined here, the barrier tends toward the lower end of the range of PMF values predicted using nonpolarizable force fields.

Incorporating polarizability into molecular simulations allows molecules to respond to different electrostatic environments. In the present study, the dipole moment of a water molecule varies upon transfer from bulk liquid to the hydrophobic lipid tail region of the

DMPC bilayer. Water dipole moments are calculated as $\mu = \sqrt{\mu_x^2 + \mu_y^2 + \mu_z^2}$ where $\mu_x = \sum_{i=1}^4 q_i x_i$ where summation is over atomic indices within a TIP4P-FQ molecule; μ_y and μ_z are defined analogously. As is common practice within the CHEQ formalism,^{11,20} we maintain charge neutrality for each water molecule via Lagrange multipliers. The magnitude of water dipole moment is not origin-dependent. For convenience we choose the system center of mass as our origin. The water dipole moment profile is shown in Figure 4. All systems studied exhibit the same dipole moment in the bulk solution and lipid interior limits ($\mu_{\text{bulk}} = 2.60$

and $\mu_{\text{interior}} = 1.88$ Debye, respectively). The bulk water dipole moment is consistent with that for pure TIP4P-FQ, although the value in the lipid interior is slightly elevated above the experimental and parameterized gas-phase dipole moment of TIP4P-FQ (1.85 D). As discussed in Reference¹¹, this increase can be due to polarization, enhanced dielectric in the lipid interior ($\epsilon \approx 2$), and long range electrostatic interactions with head-group atoms. The intermediate region between bulk water and lipid interior is noticeably different among the systems examined. These differences correlate to changes in the coordination number of water (Figure 4b). We consider two water molecules to be coordinated if they have an oxygen-oxygen distance less than 3.5 Å, which has previously been used as coordination criteria for TIP4P-FQ water.²⁸ For the CHEQ Planar system, the average coordination number decreases sharply below $z = 12$ Å; this is due to the imposed restraint that the target water molecule can not “pull in” additional water molecules beyond this distance. Correspondingly, the dipole moment decreases most rapidly as water molecules enter the lipid interior for CHEQ Planar model. The CHEQ Orig and the CHEQ Newpar systems show qualitatively similar transitions for both dipole moment and coordination number. The new parameter system shows slightly reduced coordination relative to the original parameterization, which also manifests as a slightly reduced dipole moment profile in the intermediate region. This is consistent with the increased (less favorable) hydration free energy for alkyl groups in the new parameterization.

In conclusion, we have presented results of all-atom molecular dynamics simulations of the DMPC-water interface using polarizable charge equilibration force fields. Compared to the original CHEQ DMPC force field, we see an increased potential of mean force for water molecules entering the interior of the bilayer when using a model in which the alkane groups better reproduce the experimental hydration free energy. This manifests in reduced water penetration into the bilayer interior. All polarizable systems examined in this study, however, demonstrate a reduced PMF relative to predictions from fixed-charge force fields. A water molecule's ability to reduce its dipole moment in response to the lower dielectric medium (lipid interior) is a physical effect neglected in analogous fixed-charge models that influences reduced energetic penalty in the PMF. Although the dipole moment of water approaches the experimental gas phase value, it remains slightly enhanced in the lipid interior. The enhancement is shown to behave qualitatively similar to the extent of coordination of a water molecule as it enters the lipid region. On average, a water molecule remains coordinated with at least one water molecule up until distances of 5 Å from the center of the bilayer. However, a water molecule is essentially isolated for distances less than 3 Å from the center of the bilayer. Restricting water molecules from remaining coordinated in the lipid region resulted in a 0.75 kcal/mol increase in the PMF over a comparable system in which water molecules remained coordinated. Decomposition of the PMFs shows this difference is due to less favorable water contributions in the CHEQ Planar system. Furthermore, differences in the PMF between CHEQ Newpar and CHEQ Orig are shown to result from a less favorable contribution from DMPC in the CHEQ Newpar system. The partial hydration of permeant water molecules was shown to alter the structure of the lipid membrane, consistent with the effects of water defects observed in previous studies.

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Figure 1.

Number density profiles for select headgroup atoms and water in each system studied. Peaks are identified as follows: P=Phosphorous, N=Nitrogen, O1=Single-bonded oxygen in phosphate group, O2=Double-bonded oxygen in phosphate group, OC=Carbonyl oxygens. The ratio of P:N:O1:O2:OC atoms in each DMPC molecule is 1:1:2:2:2. Density profiles were symmetrized about the center of mass of the system.

Figure 2.

Potential of mean force profiles for each system studied. Panel a compares the PMF calculated using WHAM for each system. Panels b–d compare the PMF calculated using WHAM (dashed line) and the PMF calculated from the water density profiles (solid line) for (b) CHEQ Planar, (c) CHEQ Orig, (d) CHEQ Newpar. The fraction of water-accessible volume (shown as a dotted line) is shown for comparison with the general features of the PMF.

Figure 3.

Decomposition of the potential of mean force for each system. (a) The PMF calculated via integration of forces acting on the permeant water molecule of interest. Contribution of water (b) and contribution of DMPC (c) to the PMF. All PMFs are relative to bulk water ($z = 30$ Å).

Figure 4.

(a) Average dipole moment of water as a function of its position relative to the center of mass of the system (coinciding with the bilayer interior). The experimental gas-phase dipole moment of water ($\mu = 1.85$ Debye) is shown as the horizontal dotted line. (b) Average number of water molecules coordinating a water molecule at a given z -position. A molecule is considered to coordinate another water molecule if the O-O distance is less than $3.5 \text{ \AA}$.

Table I

Potential of mean force for water penetration into the center of the DMPC lipid bilayer (relative to bulk water). All values are in units of kcal/mol. Results from calculations using WHAM, unbiased water density profiles in conjunction with Eq. 1, and from the average forces acting on the target water molecule are shown.

Model	PMF _{WHAM}	PMF _{Density}	PMF _{Forces,all}	PMF _{Forces,water}	PMF _{Forces,DMPC}
CHEQ (Planar)	5.21	∞	5.07	-1.06	6.67
CHEQ (Orig)	4.46	5.05	4.60	-2.21	6.82
CHEQ (New Par)	5.27	5.04	5.49	-2.44	7.93