Phase-transfer energetics of small-molecule alcohols across the water–hexane interface: Molecular dynamics simulations using charge equilibration models

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ABSTRACT

We study the water–hexane interface using molecular dynamics (MD) and polarizable charge equilibration (CHEQ) force fields. Bulk densities for TIP4P-FQ water and hexane, 1.0086 ± 0.0002 and 0.6378 ± 0.0001 g/cm^3, demonstrate excellent agreement with experiment. Interfacial width and interfacial tension are consistent with previously reported values. The in-plane component of the dielectric permittivity ($\varepsilon_{||}$) for water is shown to decrease from 81.7 ± 0.04 to unity, transitioning longitudinally from bulk water to bulk hexane. $\varepsilon_{||}$ for hexane reaches a maximum in the interface, but this term represents only a small contribution to the total dielectric constant (as expected for a non-polar species). Structurally, net orientations of the molecules arise in the interfacial region such that hexane lies slightly parallel to the interface and water reorients to maximize hydrogen bonding. Interfacial potentials due to contributions of the water and hexane are calculated to be -567.9 ± 0.13 and 198.7 ± 0.01 mV, respectively, giving rise to a total potential in agreement with the range of values reported from previous simulations of similar systems. Potentials of mean force (PMF) calculated for methanol, ethanol, and 1-propanol for the transfer from water to hexane indicate an interfacial free energy minimum, corresponding to the amphiphilic nature of the molecules. The magnitudes of transfer free energies were further characterized from the solvation free energies of alcohols in water and hexane using thermodynamic integration. This analysis shows that solvation free energies for alcohols in hexane are 0.2–0.3 kcal/mol too unfavorable, whereas solvation of alcohols in water is approximately 1 kcal/mol too favorable. For the pure hexane–water interfacial simulations, we observe a monotonic decrease of the water dipole moment to near-vacuum values. This suggests that the electrostatic component of the desolvation free energy is not as severe for polarizable models than for fixed-charge force fields. The implications of such behavior pertain to the modeling of polar and charged solutes in lipidic environments.

1. Introduction

Liquid–liquid interfaces appear in countless physical, chemical, and biological processes. Interfacial mechanisms and dynamics play an important role in industrial applications such as phase-transfer catalysis, electrochemical processes, liquid chromatography, solvent extraction, and interfacial absorption chemistry [1,2]. From a biological perspective, interactions of immiscible liquids at the interface are crucial to membrane processes, interactions at protein receptor sites, the transmission of neural signals, and drug delivery [2,3]. Alcohols, which are used extensively in anesthesiology, and whose toxicity is suggested to be a result of membrane interactions [4–6], are an important class of chemical compounds commonly transported across such interfaces. Moreover, they represent an ideal, prototypical system for studying the energetics of transfer between phases as a proxy for relevant biological systems such as fully hydrated phosphatidylcholine-based bilayers. Despite the prevalence of alcohol-based applications, the fundamental processes governing alcohol transport are not thoroughly understood due to the need for atomic-level resolution that is not easily attainable through experiment [7]. As a result, molecular dynamics (MD) simulation is an important tool for studying such polar–nonpolar interfaces. Indeed, much can be gained from the study of transport energetics across interfaces of polar and nonpolar species since most biological processes involve a polar solvent such as water interacting with nonpolar lipidic systems. From a theoretical standpoint, study of large nonpolar moieties can be simplified through the use of small nonpolar alkanes such as hexane. These water–alkane interfaces have been shown to provide useful models

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of the water–membrane interface [8]. To date, the majority of such simulations have utilized traditional fixed charge (nonpolarizable) force fields (see Refs. [8–12] for representative work). However, recent efforts have focused on the development of polarizable force fields, which explicitly model the effects of polarization by allowing for an explicit electrostatic response to changes in local electrostatic fields arising from changes in local chemical environment. Force fields incorporating the effects of polarization include the Drude oscillator [13,14], point-dipole [15,16], and charge equilibration (CHEQ) [17–19] models. Alcohol and hexane force fields have recently been developed within the CHEQ formalism allowing for the study of fully polarizable systems containing these species [20–22]. Certainly, a molecule's ability to modulate its charge distribution in response to its local environment is important when studying the transport energetics across the interface between fluids of vastly different dielectric responses. In addition to their biological relevance, alcohols, due to their amphiphilic nature, provide a more rigorous test of the capabilities of polarizable force fields. Therefore, we investigate the transport energetics of alcohols across the water–hexane interface utilizing polarizable force fields. Such studies are limited in the literature and serve as an important precursor to studies involving transport across solvated membranes. Furthermore, within the context of the current widespread efforts to develop polarizable force fields, the use of charge equilibration force fields for studying such systems will provide a means of comparison to the predictions of current state-of-the-art fixed-charge force fields.

This paper is organized as follows. In Section 2 we discuss the charge equilibration formalism utilized in this work to incorporate polarization into classical simulations, as well as the methods used for simulation. In Section 3 we characterize the thermodynamic and structural properties of the water–hexane interfacial system. The potential of mean force and other properties involved with phase transfer energetics of alcohols in the water–hexane interfacial system are discussed in Section 4. Finally we conclude in Section 5 with a general summary of results.

2. Force fields and computational methods

2.1. Charge equilibration force fields

The charge equilibration (CHEQ) formalism [17–19,23–29] is based on Sanderson's idea of electronegativity equilibration [28,29] in which the chemical potential is equilibrated via the redistribution of charge density. In a classical sense, charge density is reduced to partial charges, Q_i, on each atomic site. The electrostatic energy for a system of M molecules containing N atoms per molecules is then expressed as

$$E_{\text{electrostatic}} = \sum_{k=1}^{M}\sum_{i=1}^{N}\chi_{ik}Q_{ik} + \frac{1}{2}\sum_{l=1}^{M}\sum_{\alpha=1}^{N}\sum_{\beta=1}^{N}\eta_{\alpha l,\beta l}Q_{\alpha l}Q_{\beta l}$$
$$+ \frac{1}{2}\sum_{i=1}^{MN}\sum_{j=1}^{MN}\frac{Q_iQ_j}{r_{ij}} \tag{1}$$

where the χ's are the atom electronegativities which control the directionality of electron flow and the η's are the atomic hardnesses which control the resistance to electron flow to or from an atom. Although these parameters derive from the definitions of electron affinity and ionization potential, they are treated as empirical parameters for individual atom types. Heterogeneous hardness elements that describe the interaction between two different atom types are calculated using the combining rule [30] on the parame-

terized homogeneous hardness elements:

$$\eta_{ij}(R_{ij},\eta_i,\eta_j) = \frac{(1/2)(\eta_i+\eta_j)}{\sqrt{1.0+(1/4)(\eta_i+\eta_j)^2R_{ij}^2}} \tag{2}$$

where R_{ij} is the distance between atoms i and j. This combination locally screens Coulombic interactions, but provides the correct limiting behavior for atomic separations greater than approximately 2.5 Å. The standard Coulomb interaction between sites not involved in dihedral, angle, or bonded interactions with each other is included as the last term in Eq. (1). The second term in Eq. (1) represents the local charge transfer interaction, which is usually restricted to within a molecule or an appropriate charge normalization unit, i.e., no intermolecular charge transfer. Charge is constrained via a Lagrange multiplier, λ, which is included for each molecule, resulting in the electrostatic energy expression:

$$E_{\text{electrostatic}} = \sum_{k=1}^{M}\sum_{i=1}^{N}\chi_{ik}Q_{ik} + \frac{1}{2}\sum_{l=1}^{M}\sum_{\alpha=1}^{N}\sum_{\beta=1}^{N}\eta_{\alpha l,\beta l}Q_{\alpha l}Q_{\beta l}$$
$$+ \frac{1}{2}\sum_{i=1}^{MN}\sum_{j=1}^{MN}\frac{Q_iQ_j}{r_{ij}} + \sum_{j=1}^{M}\lambda_j\left(\sum_{i=1}^{N}Q_{ji} - Q_j^{\text{Total}}\right) \tag{3}$$

We remark that use of multiple charge normalization units can modulate molecular polarizability by limiting intramolecular charge transfer to physically realistic distances. Such an approach controls previously observed superlinear polarizability scaling [20,31,32], which also manifests as the polarization catastrophe (as observed in point polarizable force fields) [16,32], while developing a construct for piecing together small molecular entities into macromolecules. The molecular polarizability within this formalism can be derived as

$$\alpha_{\gamma\beta} = \mathbf{R}_\beta^t\eta'^{-1}\mathbf{R}_\gamma \tag{4}$$

where η' denotes the molecular hardness matrix *augmented* to incorporate total charge constraints for each charge normalization unit [32]. $\mathbf{R}_\beta$ and $\mathbf{R}_\gamma$ represent the β and γ Cartesian coordinates of the atomic position vectors, respectively.

Charge degrees of freedom are propagated via an extended Lagrangian formulation imposing a molecular charge neutrality constraint, thus providing for electronegativity equilibration at each dynamics step. The system Lagrangian is:

$$L = \sum_{i=1}^{M}\sum_{\alpha=1}^{N}\frac{1}{2}m_{i\alpha}\left(\frac{dr_{i\alpha}}{dt}\right)^2 + \sum_{i=1}^{M}\sum_{\alpha=1}^{N_i}\frac{1}{2}m_{Q,i\alpha}\left(\frac{dQ_{i\alpha}}{dt}\right)^2 - E(Q,r)$$
$$- \sum_{i=1}^{M}\lambda_i\sum_{\alpha=1}^{N_i}Q_{i\alpha} \tag{5}$$

where the first two terms represent the nuclear and charge kinetic energies, the third term is a potential energy, and the fourth term is the molecular charge neutrality constraint enforced on each molecule i via a Lagrange multiplier λ_i. The fictitious charge dynamics are determined using a charge "mass" with units of (energy time^2/charge^2). This is analogous to the use of an adiabaticity parameter in fictitious wavefunction dynamics in Car Parinello (CP) type methods [33]. Charges are propagated based on the forces arising from differences between the average electronegativity of a molecule and the instantaneous electronegativity at an atomic site.