Interaction of alcohols and anesthetics with the water–hexane interface: a molecular dynamics study

Abstract The transfer of eight solutes across the water–hexane interface is studied using molecular dynamics computer simulations. Four of these solutes are model amphiphiles, straight chain alcohols – methanol, ethanol, butanol and hexanol. The remaining four molecules – cyclopropane, nitrous oxide, isoflurane and desflurane – are non-amphiphilic and polar or weakly polar. All of them are clinical anesthetics. All eight molecules exhibit free energy minima at the interface, indicating that they are interfacially active. Whereas interfacial activity of amphiphiles has been well known, it is shown here that a similar, although somewhat weaker behavior is also characteristic of a wide range of polar solutes. This can be explained as a balance between electrostatic and non-electrostatic contributions to the free energy, that change monotonically, but oppositely near the interface. Qualitatively, similar results are expected for solutes at interfaces between water and other non-polar liquids or lipid bilayers. Based on the results showing a very good correlation between anesthetic potencies and interfacial concentrations of 20 anesthetic compounds, it is proposed that the site of anesthetic action is located near the interface between water and the neuronal membrane.

Keywords Water – hexane interface – straight chain alcohols – anesthetics – computer simulations

Introduction

Interfaces between water and non-polar phases are of considerable interest as environments for heterogeneous catalysis, as well as many important electrochemical and photochemical processes [1–3]. Emerging new industrial applications involve the building up of layers of monomolecular films at interfaces [4, 5]. In biological systems, interactions of small molecules and peptides with water–membrane interfaces and protein receptor sites near these interfaces are highly relevant for modulation of receptor action, signal transduction [6, 7] and membrane fusion [8]. Studies in all these areas require knowledge of the principles determining the behavior of small molecules in interfacial environments. These principles, however, are not very well understood. Recently, considerable progress in this direction has been achieved by applying computer simulation methods to interfacial systems [9, 10]. In this paper, this line of research is continued.

A compound is interfacially active when its concentration in the interfacial region exceeds those in the two adjacent bulk phases. In the limit of infinite dilution, interfacial activity can be identified by the presence of an interfacial minimum in the free energy of the solute, as a function of its position along the direction perpendicular to the interface. Traditionally, activity at the interface between water and a non-polar liquid has been associated with the concept of amphiphilicity. In an interfacial environment, the polar parts of amphiphilic solutes are
immersed in water while their non-polar parts are buried in the non-polar phase. Straight chain alcohols and fatty acids are examples of amphiphilic molecules. Although amphiphilicity is sufficient to ensure interfacial activity, it is not a necessary condition. In recent theoretical studies [11-13], a wide range of polar, but not amphiphilic molecules, have been predicted to accumulate at the interface.

In this paper, we discuss the behavior of eight solutes at the interface between two immiscible liquids - water and hexane. Four of the solutes, methanol, ethanol, butanol and hexanol, are amphiphilic, straight chain alcohols. This choice allows us to examine systematically the interfacial activity of amphiphiles as a function of the hydrophobic chain length. The remaining four molecules, nitrous oxide, cyclopropane, isoflurane and desflurane are not amphiphilic. Even though nitrous oxide, cyclopropane and the two halogenated ethers are structurally unrelated, they, nonetheless, share an important property - all of them are clinical anesthetics.

We have two main objectives. The first is to understand the general principles that determine the activities, orientations and conformational equilibria of small solutes at interfaces between water and non-polar media. Once these principles are established, they can be applied to predict the interfacial behavior of different solutes, not only at simple liquid-liquid interfaces, but also in more complex systems, such as water-membrane interfaces.

The second objective is to apply our knowledge of interfacial systems to a concrete problem of considerable medical interest - the determination of a relationship between the interfacial behavior of anesthetics and their anesthetic activity. This represents an alternative view to the century-old Meyer–Overton hypothesis [14, 15], which relates anesthetic activity of anesthetics to their solubility in the bulk oily phase.

**Method**

**Description of the system**

The system consisted of 480 water molecules in a lamellar arrangement located between two lamellae of hexane, each containing 80 molecules. As can be seen in Fig. 1, two water–hexane interfaces were present in this system. Liquid hexane was in equilibrium with its gas phase, yielding two liquid–vapor interfaces. The x,y-dimensions of the simulation box, parallel to the interfaces, were 24 × 24 Å and the z-dimension, perpendicular to the interfaces, was 150 Å. The approximate widths of the water, and each of the hexane lamellae, were 25 and 32 Å, respectively.

**Potential energy functions**

In the molecular dynamics simulations presented here, the energies of the solute molecules were evaluated using an empirically based Hamiltonian, $H_{\text{total}}$, which consisted of a sum of individual contributions arising from bond stretching, deformation of valence and torsional angles, as well as Lennard–Jones and Coulomb interactions between