

Vapor-liquid interface properties of diethyl sulfoxide-water and ethyl methyl sulfoxide-water mixtures: Molecular dynamics simulations and quantum-chemical calculations



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ABSTRACT

Senior sulfoxides, such as diethyl sulfoxide (DESO) and ethyl methyl sulfoxide (EMSO), are prospective cryoprotectants. These liquids are either applied in the form of their mixtures with water or mix with water inside the living cell. This work reports vapor-liquid equilibrium (VLE) properties of the senior sulfoxide-water mixtures over an entire composition range. Negative deviations from an ideal behavior were found for both sulfoxides in their aqueous mixtures. The inter-molecular interactions in the mixtures are predominantly electrostatic. A strong hydrogen bond exists between DESO (EMSO) and water, whereas water does not coordinate the methylene groups. Thanks to their hydrophobic chains, DESO and EMSO exhibit elevated densities at the vapor-liquid interface. Both DESO and EMSO act rather efficiently as surfactants decreasing surface tension of the water-rich mixtures. The reported results confirm stability of the aqueous mixtures of sulfoxides and foster their emerging applications.

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1. Introduction

Diethyl sulfoxide (DESO) and ethyl methyl sulfoxide (EMSO) are senior sulfoxides (Fig. 1), whose physical chemical properties suggest their prospective applications in cryoprotective systems [1–6]. Experimental evidence at the laboratory level exists that cryoprotective performance of DESO is better than that of dimethyl sulfoxide (DMSO) [1]. While DMSO continues to be widely applied in medicine, biology, and organic synthesis as one of the major polar aprotic solvents [7–19], emergence of new sulfoxides may, to some extent, substitute DMSO. DMSO exhibits low toxicity to animals, including human beings. The lethal dose of DMSO is larger than that of ethanol. Therefore, applications of DMSO in medicine and pharmacy are extremely versatile and will probably remain so. One would assume that DESO and EMSO are somewhat friendlier to living cells due to possessing a bit longer hydrocarbon chains. This feature favors penetration through lipid bilayers [1], although energetic characteristics of this process have not been provided yet.

DMSO and DESO can be obtained with an outstanding degree of purity providing cryopreservation of cells and tissues. Based on the recent atomically-precise simulations [6], EMSO occupies an

intermediate position between the two above solvents. The successful synthesis of EMSO or the corresponding synthesis attempts, however, have never been reported. Consideration of EMSO in simulations is also worthwhile and may stimulate experimental efforts. According to Markarian and coworkers [1], DESO is able to create an amorphous, glassy solid state in its mixtures with water. Cryoprotectants help to avoid ice crystals making freezing and thawing of biological entities more sustainable. Based on the calorimetric melting peaks [1], addition of DESO to water decreases its melting point by ca. 20 K, which is less than an effect of DMSO, ca. 70 K.

DESO exhibits strong self-associative effects, which are even stronger than those in DMSO. Markarian and coworkers, who systematically pioneered the field of senior sulfoxides, suggested strong intermolecular association in liquid DESO, including formation of the $S=O \cdots H-C$ hydrogen bonds [20,21]. In turn, recent hybrid density functional theory (DFT) calculations [6] revealed that the dipole moments of sulfoxides are 3.34 D (DMSO), 4.53 D (EMSO), 4.64 D (DESO), and 4.83 D (dipropyl sulfoxide, $(C_3H_7)_2SO$). The dipole moments were computed for isolated molecules in vacuum and may slightly increase if polarizable continuum models (implicit solvation) are used. A larger dipole moment indicates stronger charge-dipole interactions between the solute and the solvent, e.g. between sulfoxides and water. Indeed, mixtures of

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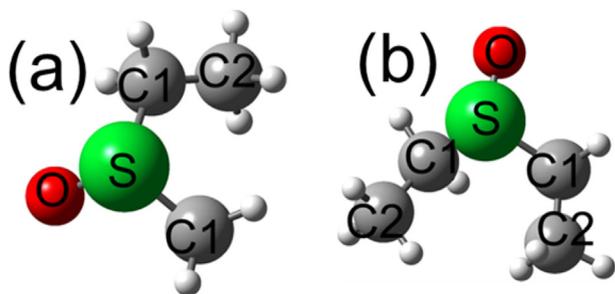


Fig. 1. Optimized spatial structures of molecules: (a) EMSO and (b) DESO. Carbon atoms are grey, hydrogen atoms are white, oxygen atoms are red, sulfur atoms are green. The calculations were conducted at the hybrid density functional theory level of theory M06/6-311 + G*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

DESO with water exhibit strongly negative deviations (stronger than in the DMSO-water mixtures) from an ideal behavior [4,22,23].

Investigation of the vapor-liquid equilibria (VLE) provides a lot of useful information, since VLE properties directly depend on the inter-molecular interaction in the studied pure liquid or liquid mixtures. Analysis of the saturated vapor pressure vs. molar fraction of the admixture allows for characterization of solution deviations from ideality. It also assesses mutual miscibility of two liquids. In the present paper, I report simulation results of the DESO-water and EMSO-water VLEs. The discussion is started with the basic VLE properties, such as saturated vapor pressure, being continued with structure and thermodynamics of the mixtures. The simulated saturated vapor pressures were compared to the available vapor pressures of DESO-water mixtures in the range 293.15–303.15 K [22], whereas all properties of the EMSO–water mixtures are provided here for the first time. Saturated vapor pressure in the dimethyl sulfoxide – water mixtures was reported elsewhere [24].

2. Methods

Simulations of VLEs were accomplished by the classical molecular dynamics (MD) method using a sum of pairwise non-polarizable interaction potentials. The DESO and EMSO models were represented in the framework of the united-atom approximation, as recently derived and validated elsewhere [6]. The water molecules were simulated by means of the SPC/E model, in its GROMOS96 compatible version [25,26].

The MD systems (Table S1) were equilibrated at target temperature and constant pressure (1 bar) to attain natural density. The pure water systems contained 1500 molecules, while the sulfoxide-water systems contained 1000 molecules. Furthermore, larger systems, 6000 molecules, were simulated for the 10% DESO/EMSO-water mixtures to characterize the vapor-liquid interface structure. Subsequently, the length of one of the box sides (z-direction) was extended up to 50–60 nm. In this way, an interface was created (Fig. 2) between a relatively thin infinite liquid film (due to

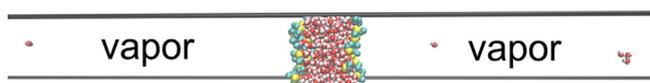


Fig. 2. Example of the simulated vapor-liquid equilibrium obtained after 80 ns of continuous equilibrium MD simulation. Sulfur atoms are yellow, oxygen atoms are red, hydrogen atoms are white, ethyl and methyl chains are cyan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

periodicity in the XY plane) and vacuum. Significant space was provided for saturated vapor of the mixture to occupy. The MD simulations were conducted in the constant temperature constant volume ensemble to observe formation and existence of VLE in real-time. Fluctuations of pressure in the nanoscale systems are inherently very large leading to uncertainties of the results. Estimation of small pressures ($\ll 1$ bar) requires significant sampling of the phase space. If intramolecular contributions are included in the pressure profile, an estimation of the saturated vapor pressure is possible using the bulk liquid phase. Upon equilibrium, pressures in the liquid phase and in the vapor phase are equal. Different methodologies and challenges to obtain realistic interface properties were applied and discussed elsewhere [27] using ethane and other hydrocarbons as an example. Instead of simulating at low temperatures, it is possible to estimate vapor pressures at a few temperatures near the boiling point (requires shorter MD runs) and fit $p_{\text{sat}} = f(T)$ to the three-parameter Antoine's equation. Subsequently, extrapolation can be performed to the desired temperature range. Note that the Antoine's equation normally requires different empirical parameters above and below the boiling point of each liquid.

The equations-of-motion were integrated by the velocity Verlet propagation algorithm with an integration time-step of 1.0 fs. Upon MD, the energy components were saved every time-step for subsequent averaging and statistical processing. Immediate coordinates were saved every 10 000 time-steps using multiplier 1000 in the XRD routine. Electrostatic interactions were simulated directly (by the Coulomb law) if the distance between any two interaction centers were smaller than 0.9 nm. If the distance exceeded 0.9 nm, the reaction-field-zero technique was employed. These methodological parameters are pre-determined by the choice of the force field. Constant temperature was maintained by the velocity rescaling thermostat of Bussi, Donadio, and Parrinello with a relaxation time constant of 500 fs. [28]. The corrections for the long-range dispersion forces were included in the calculated energy and pressure.

The MD simulations (Table S1) were carried out in the GRO-MACS 4 molecular dynamics engine [29] supporting highly parallel setups. Parallelization was achieved using the particle decomposition scheme. The list of neighboring molecules was updated every 10 time-steps within the radius of 1.0 nm. The trajectories were visualized in the VMD 1.9 (Visual Molecular Dynamics) software [30]. Gabedit [31] and Packmol [32] were used to manipulate molecular structures and prepare initial configurations for MD simulations.

Ab initio calculations were conducted at the M06 hybrid density functional theory (DFT), since it accurately reproduces non-covalent interactions [33]. The atom-centered split-valence double-zeta polarized basis set 6-31G(d) was used for all computations. The self-consistent field convergence criterion was set to 10^{-8} Hartree. The local minimum was considered to be found when the largest force in the system was smaller than $0.4 \text{ kJ mol}^{-1} \text{ nm}^{-1}$. 130 initial configurations of DESO (EMSO) and water molecules were randomly generated to investigate possible local-minimum states.

3. Results and discussion

Accurate computer simulation of VLE is challenging. A saturated vapor must contain enough particles for proper sampling. In turn, a liquid film must remain integral despite molecules, which continuously leave its surface. To estimate suitable sampling times for sulfoxide-water VLEs, preliminary calculations were conducted (Fig. 3). Equilibration of VLE takes significant time, even though liquid phase is essentially equilibrated. According to Fig. 3, the

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