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Calculation of the intrinsic solvation free energy profile of methane across a liquid/liquid interface in computer simulations

Mária Darvas [a],*, Miguel Jorge [b], M. Natalia D.S. Cordeiro [c], Pál Jedlovszky [d,e,f]

[a] SISSA, Sector of Molecular and Statistical Biophysics, 265 via Bonomea, 34136 Trieste, Italy
[b] Department of Chemical and Process Engineering, University of Strathclyde, 75 Montrose Street, Glasgow G1 1XJ, United Kingdom
[c] REQUIMTE, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal
[d] Laboratory of Interfaces and Nanosize Systems, Institute of Chemistry, Eötvös Loránd University, Pázmány P. stny 1/A, H-1117 Budapest, Hungary
[e] MTA-BME Research Group of Technical Analytical Chemistry, Szt. Gellért tér 4, H-1111 Budapest, Hungary
[f] EKF Department of Chemistry, Leányka utca 6, H-3300 Eger, Hungary

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ABSTRACT

The transfer of ions and neutral particles through water/organic interfaces has been widely studied in the last few decades by both experimental and theoretical methods. The reason for the never ceasing interest in this field is the importance of transport phenomena in electrochemistry, biochemistry and separation science. In the current paper the solvation Helmholtz free energy profile of a methane molecule is presented, with respect to the intrinsic (i.e., real, capillary wave corrugated) interface of water and 1,2-dichloroethane, as obtained from constrained molecular dynamics simulations. The results of the current calculation are analysed in comparison with the solvation free energy profile of the chloride ion across the same interface.

1. Introduction

The transport of ions and neutral penetrants across fluid interfaces (liquid–liquid, liquid-vapour interfaces or lipid membranes) are widely studied model cases of biologically important processes such as the transfer of drugs across the cell membrane [1–5]. The driving force and mechanism of these processes can be interpreted in the framework of statistical thermodynamics, supposing that the free energy profile of the transport phenomenon is known at reasonable resolution. Several experimental techniques, such as calorimetry, voltammetry, or their various combinations [6–10] are aimed at measuring the free energy difference between two states, e.g., a solvated and a non-solvated one, or two different solvated states. Nevertheless, the free energy profiles are only reproducible by the so-called single molecules optical tweezers experiments in special cases involving physico-chemical processes of biomacromolecules, such as DNA or RNA unwinding or protein folding [11].

In principle, computer simulation methods, such as molecular dynamics (MD) or Monte Carlo can be used to obtain the free energy profile along a carefully chosen reaction coordinate, since, in an ideal case, unbiased simulations can provide a set of sample configurations representing a given statistical mechanical ensemble. In the case of the canonical ensemble, the $\rho(\xi)$ density profile of the microstates along the reaction coordinate ξ can be converted into the Helmholtz free energy profile, $A(\xi)$, according to the equation:

$$A(\xi) = -RT \ln\rho(\xi) \tag{1}$$

where R and T stand for the gas constant and absolute temperature, respectively. In practice, however, the microstates belonging to ξ values characterized by high potential energy are poorly represented in the sample due to the finite length of the simulation. This makes direct counting inaccurate in estimating the free energy of these states, including important features such as high energy transition states. This statistical unreliability calls for the use of enhanced sampling methods, developed to capture rare events, in which the system is restrained by a biasing potential to the reaction coordinate of interest. These methods include harmonic [12] and adaptive umbrella sampling [13], steered MD [14], metadynamics [15], potential of mean force (PMF) calculation by, e.g., the constrained MD algorithm [16,17], or the Widom test particle insertion method [18] and its cavity insertion variant [19]. For solvation free energy profile calculations across fluid interfaces, these methods have been widely used for a number of non-ionic [19–28] and ionic penetrants [29–44] at various fluid interfaces.

The question of the sampling efficiency is not the only difficulty one has to face when calculating solvation free energy profiles across fluid interfaces in computer simulations. The other major problem comes from the fact that any fluid interface is corrugated, on the

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* Corresponding author.
E-mail address: mdarvas@sissa.it (M. Darvas).

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atomistic length scale, by dynamic fluctuations due to the presence of thermal capillary waves [45]. Substituting this capillary wave corrugated real surface (often referred to as the "intrinsic" surface of the given phase) by an ideally flat ("non-intrinsic") one, such as the Gibbs dividing surface, leads to a systematic error of unknown magnitude in calculating any interface-related property if the system is seen at atomistic resolution. This systematic error originates from the misidentification of a number of surface molecules as being in the bulk phase and vice versa. Further, the calculation of any profile along the macroscopic interface normal axis implies averaging the quantity of interest in slabs that are at a given distance from the interface. The error coming from the incorrect location of the interface along its macroscopic normal axis when it is estimated by a mathematical plane leads to incorrect distance values, and hence to a systematic error in the calculated profiles. Thus, for instance, it has been shown several times that the sigmoidal-like, non-intrinsic density profile of the molecules constituting a given phase turns into a profile exhibiting several minima and maxima (as akin to typical radial distribution functions) if the profile is calculated relative to the real, molecularly rough intrinsic surface rather than to an external coordinate [46–52]. Therefore, any physically meaningful calculation of the solvation free energy profile across fluid interfaces requires that it is determined *relative to this molecularly rugged surface* rather than to an external axis (or, equivalently, relative to an ideally flat planar surface), as it has been done in most studies.

In order to perform such calculations, one has to be able to reconstruct the exact position of the surface in every frame. This task is equivalent to identifying the full set of interfacial molecules for every saved configuration. The first attempt to perform such an analysis was made three decades ago by Stillinger, who stated that interfacial molecules differ from bulk phase ones in the sense that they are in direct contact with a percolating volume of empty space [53]. This approach, though theoretically correct, was never routinely used due to the enormous computational demand of its algorithm. More than 20 years later, Chacón and Tarazona developed their self-consistent Intrinsic Sampling Method, which attempts to find the covering surface that goes through at a set of pivot atoms and the area of which is minimal [46]. Others tried to approximate the intrinsic interface by dividing the system into several slabs along the macroscopic surface normal axis, using a mesh with a resolution comparable with the capillary wave length, and defined the position of the interface in each slab separately [22,31,54–57]. This method has been further elaborated by Jorge and Cordeiro, who proposed to use a considerably finer grid, and determined the number of slabs required for convergence [49]. Yet another method, called Identification of the Truly Interfacial Molecules (ITIM) has been developed recently by Pártay et al. [58]. In ITIM analysis a probe sphere of a given radius, R_p, is moved along test lines from the bulk opposite phase towards the surface of the phase to be analysed. Once it touches the first molecule of the phase of interest, it is stopped, and the touched molecule is marked as being interfacial. The intrinsic surface itself is then approximated by the positions of the interfacial molecules. A completely different method, based on the relative distance between molecules of opposing phases has been proposed by Chowdhary and Ladanyi for liquid–liquid interfaces [48]. Finally, several intrinsic surface analysis methods that are free from the assumption that the interface itself is macroscopically planar, and thus more generally applicable, have been developed in the past few years [59–61]. A recent comparison of the various intrinsic surface determining techniques revealed that ITIM provides an excellent compromise between accuracy and computational cost [62].

Even with a relatively efficient interface analysis method at hand it is computationally demanding to perform an intrinsic analysis of the free energy profile of transfer, since the biased simulation itself requires greater computational resources than an unbiased one. In a previous paper [44] we have proposed a computationally feasible way of calculating the intrinsic solvation free energy profile of a single penetrant particle across fluid interfaces and applied it for the calculation of the intrinsic solvation free energy profile of a Cl^- ion across the water–1,2-dichloroethane (DCE) liquid–liquid interface. In the current paper we report the analysis of the intrinsic solvation Helmholtz free energy profile of a neutral penetrant, namely methane, across the same liquid–liquid interface in comparison with the features of the ionic penetrant. As for the case of the chloride ion [44], we compute here the intrinsic methane free energy profile relative to the surface of the water phase.

The paper is organized as follows. In Section 2 details of the computer simulations, intrinsic surface analysis and free energy calculations are given. In Section 3, the intrinsic free energy profile is presented in comparison with the corresponding non-intrinsic profile, and compared also to the intrinsic solvation free energy profile of the Cl^- ion across the same interface. Finally, in Section 4 the main conclusions of this study are summarised.

2. Computational details

2.1. Simulation of the interfacial system

Molecular dynamics simulations of the water–DCE liquid/liquid interfacial system containing one methane molecule at different, suitably chosen positions were performed on the canonical (N,V,T) ensemble at 298 K using the GROMACS 3.3.2 simulation program package [63]. The lengths of the X, Y and Z edges of the rectangular basic simulation box (X being perpendicular to the macroscopic plane of the interface) were 104, 50 and 50 Å, respectively. The system consisted of 4000 water, 1014 DCE, and one methane molecules.

The water molecules were described by the TIP4P potential [64], whereas standard united atom OPLS parameters were used to model methane and DCE [65]. All bond lengths and bond angles were kept fixed in the simulations, while torsional flexibility of the DCE molecule around its C – C bond was allowed. The interaction and geometry parameters of the potential models used are summarised in Tables 1 and 2, respectively. The methane molecule as well as the CH_2 groups of the DCE molecules were treated as united atoms. The total potential energy of the system was assumed to be the sum of the interaction energies of all molecule pairs. The interaction energy between two molecules was expressed as the sum of Lennard–Jones and Coulomb terms acting between the interaction sites and their partial charges. Bond lengths and angles of the DCE and water molecules were kept rigid by means of the LINCS [66] and SETTLE [67] algorithms, respectively. The pairwise interactions were calculated explicitly within a centre–centre cut-off distance of 9.0 Å. Beyond this distance, Lennard–Jones contributions were truncated to zero, whereas the long range part of the electrostatic interactions was accounted for using the Particle Mesh Ewald (PME) method [68]. The temperature of the system was kept constant using the Nosé–Hoover thermostat [69,70]. The equations of motion were solved using the integration time step of 1 fs.

Table 1
Potential parameters of the water, DCE, and methane molecules.

Molecule	Interaction site	σ/Å	ε/kJ mol^{-1}	q/e
Water[a]	O_W	3.154	0.649	0.000
	H_W	0.000	0.000	0.520
	M_W[b]	0.000	0.000	−1.040
CH_4[c]	CH_4	3.730	1.229	0.000
DCE[c]	CH_2	3.800	0.494	0.227
	Cl	3.400	1.255	−0.227

[a] TIP4P model, ref. [64].

[b] Non-atomic interaction site, placed along the H – O – H bisector 0.15 Å away from the O atom toward the hydrogens.

[c] Lennard–Jones parameters correspond to the OPLS model, ref. [65], fractional charges are taken from ref. [55].