Potential of Mean Forces of Solutes in Water by Modified Solvent-accessible Surface Method

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We propose an empirical method for evaluating the potential of mean force (p.m.f.) of solutes in water by modifying the solvent-accessible-surface (SAS) method described by Eisenberg et al. In addition to the SAS energy, the energy required to generate an excluded volume between adjacent solute molecules and the energy contribution due to coulomb interactions are accounted for in the proposed method. The proposed method was examined on the p.m.fs of methane-methane in water and successfully reproduced the p.m.fs. This method is basically applicable to general molecular interactions, such as protein-protein interactions in water.

We show a new empirical method for evaluating the potential of mean force (p.m.f.) [1] of solutes in water by taking into account the energy contribution of generating an excluded volume between adjacent solute molecules on the SAS method.[2] First we calculated the p.m.f. of a methane pair in water by molecular dynamic (MD) simulation by slow-growth free energy perturbation method at 300K with 670 TIP3P water molecules and a periodic boundary condition. Based on MD simulations by us and other scientists,[3,4] we derived an empirical method to calculate the p.m.f. for several atoms, here carbon and oxygen. The p.m.f. is a function of the intermolecular distance, and its gradient provides the force acting on two solute molecules. The p.m.f. can be decomposed into two parts, [1]direct interactions between solutes and [2] the effects of the solvent around solutes at arbitrary distance from infinite separation. In this paper, the former is decomposed into the coulombic interaction, E_c, and the energy from the sum of the van der Waals interaction, E_{vdw}, while the latter is given by the SAS energy, E_{SAS}, and the energy for making a void volume, E_{void}. Then solvents are not explicitly appeared in the modified SAS method. In vacuum both E_{SAS} and E_{void} become zero.

$$E_{total} = E_c + E_{SAS} + E_{void} + E_{vdW}. \tag{1}$$

E_c, is given by the sum of Debye-Hückel type potentials for the atom-centered point charges of solute molecules. It may be small for hydrophobic solutes but generally it should be took into account because of the effects of dipoles or quadrupoles. By definition, E_{SAS} is the sum of the SAS energy of each atom which forms the solute molecule,

$$E_{SAS} = \sum_i \sigma_i * A_i \tag{2}$$

where A_i is the SAS of each atom and σ_i is an atomic solvation parameter. σ_i's must be reconstructed while accounting for E_c and E_{void}. As two solute molecules (or atoms) approach each other, the water molecules between the solutes must be excluded. Since the process of generating a void requires that the bonds between water molecules be broken, the energy necessary to break these intermolecular bonds must be considered. The energy required to form the void, E_{void}, is written as

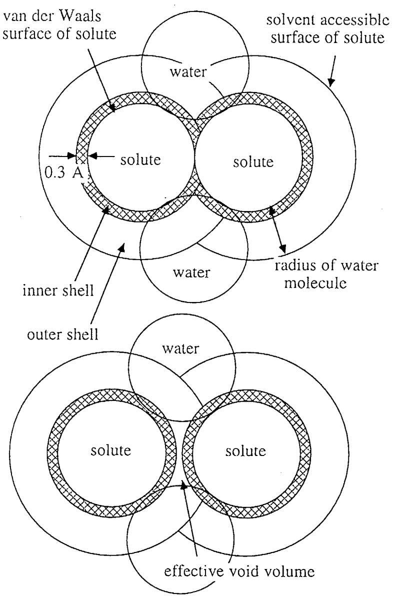

Figure 1. Schematic representation of the void volume in a solution. The shaded shells and the open shells represent the inner and outer shells, respectively. The interstice surrounded by the two shaded shells and water molecules is the effective void.

$$E_{void} = \theta * v. \tag{3}$$

where θ is the energy required to form a void of unit volume and v is the void volume. We assumed that θ is constant and independent of the void shape. For water, θ is 0.54 kcal/cm^3 which is the latent heat of vaporization. Figure 1 shows our method of approximating the void volume. A water molecule is approximated by a sphere with a radius of 1.4 Å. We paid attention to the shell between the vdW surface of solute and its solvent-accessible surface. We divided this shell into two shells: the outer shell and the inner shell. The latter is shown by shading in Figure 1. Since a solvent molecule contacts with the solute at a point on the vdW surface, the inner shell is always void-rich. We use the void volume in the outer shells as the effective void volume for the p.m.f.calculations. When two solutes are in contact, the molecules are closely packed and the effective void volume must be zero. Taking this fact into account, we found that the appropriate depth of the inner shell is approximately 0.3 Å for water. E_{SAS} and E_{void} are numerically calculated using finite element model. The E_{vdW} was approximated as the sum of exponential type potential functions,

$$E_{vdW} = c_1 * \sum_{i<j} \exp(-c_2 * (r_{ij} - (\rho_i + \rho_j))), \tag{4}$$

where the ρ_i and ρ_j stand for the vdW radii of atom i and atom j.

Eq.(4) was used to realize the repulsion force between solutes. The reason why attractive force of vdW was omitted in our calculation is as follows: vdW interaction between solutes is more or less the same as that between solute and solvent molecule surrounding the solute. Then we avoided meaningless complication in our convenient evaluation method and took into account only the excluded effect in solute-solute collision with the exponential expressions. In the simplest case we can use hard sphere model for the solutes since the hardness of the sphere is not so essential for the p.m.f. reproduction compared to the solute-solute interactions through solvent. The schematic representation of these four interactions is shown in Figure 2.

c1, c2 and σ_i's were determined by fitting to the p.m.fs of a methane pair obtained by our MD simulation as c1=0.2, c2=5, and σ = 20 for carbon atom and 4 for oxygen atom in cal/Å^2/mol. vdW radii of carbon and water were 2.0 and 1.4 Å, respectively. Here, the "carbon atom" and "oxygen atom" include the attached hydrogen atoms and they are approximated as sphere. Figure 3 shows the p.m.fs obtained by the modified SAS method comparing with the MD results. The p.m.fs of C-C, C-O, and O-O obtained by the modified SAS method agreed with the MD results by van Belle et al,[3] Levy et al [4] and by us. The p.m.f.by the original SAS method is also shown in Figure 3 as a simple straight line because of the reduction of the total SAS of solute-pair by overlapping their solvent accessible surfaces. The most convenient point of the proposed method is that if we obtain the atomic solvation parameters for atoms composing molecules to be tested we are able to calculate the p.m.fs in solvent. Since we do not calculate explicitly the forces acting on the solutes from solvents the computing time becomes very much reduced.

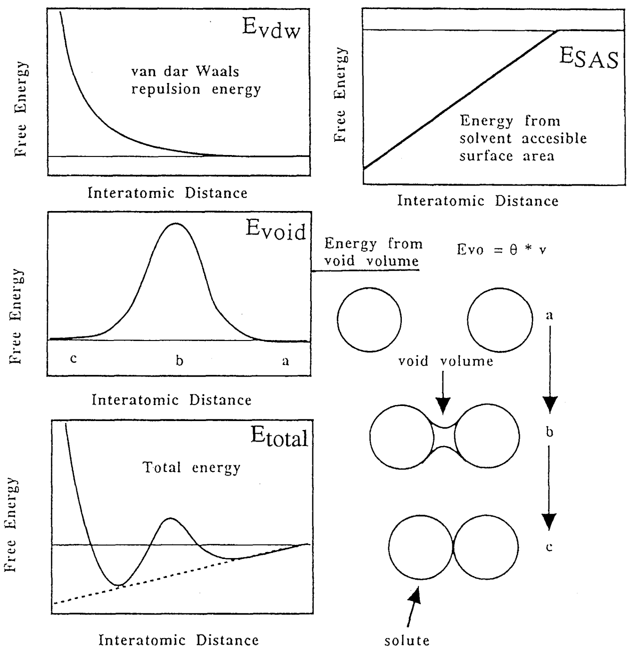

Figure 2. Schematic representation of E_{vdw}, E_{SAS} , Evoid and E_{total}. E_c is not shown here.

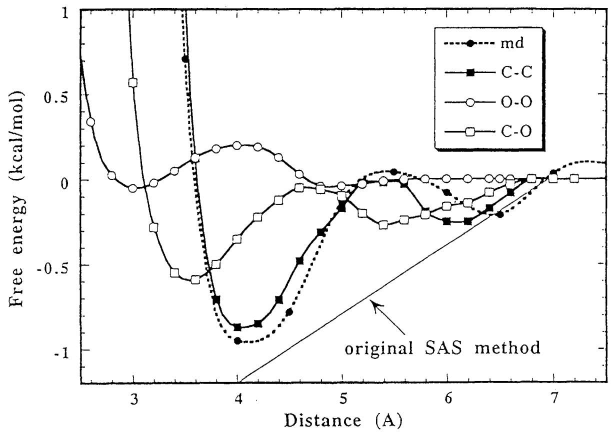

Figure 3. Comparison of the p.m.fs in water by this empirical method and MD.The dotted ("md") and solid lines stand for the p.m.f of methane pair by MD and that by the original SAS method, respectively. The "C-C","O-O" and "C-O" stand for the p.m.fs of methane-methane, water-water and methane-water pairs by the empirical method, respectively.

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