Comparison Between Force Field-Based Implicit Solvent Models and DFT/SCRF for Protein–Surface Interactions

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Statement of Purpose: Implicit treatment of the solvation effects in the empirical force field-based molecular simulations allows large protein-surface systems to be simulated efficiently. However, many current implicit solvent models were developed for the simulation of peptide or protein behavior in solution alone, and thus may not be appropriate for protein interactions with synthetic material surfaces. With the presence of a large material surface, the fundamental property that must be represented in the implicit solvent models is the change in energy as a given peptide residue approaches a given type of surface. The objective of this research was to use density functional theory (DFT) combined with the self-consistent reaction field (SCRF) implicit solvation method[1] to obtain a base-line set of relationships that characterizes the change in free energy versus surface-separation distance (*SSD*) for a series of peptide residue-surface systems for comparison with similar simulations using four different implicit solvent models with the CHARMM force field[2].

Methods: Four representative protein residues: Val, Ser, Asp, and Lys, were placed in between of two Gly residues to form three-residue short peptides in α-helix conformations. (Fig. 1(a)). Three SAM surfaces were created with different terminating functional groups, i.e., CH_3, OH, and COO^-/COOH (Fig. 1(b)). Twelve different molecular systems were therefore obtained by the combination of the four peptides and three functionalized SAM surfaces. For each molecular system, changes in adsorption free energy (ΔG_{ads}) when the peptide approaches the surface as a function of surface-separated distance (*SSD*) were calculated by DFT/SCRF and four implicit solvent models (ACE[3], ASP[4], EEF1[5] and RDIE[6]) combined with the CHARMM 19 (C19) force field[2].

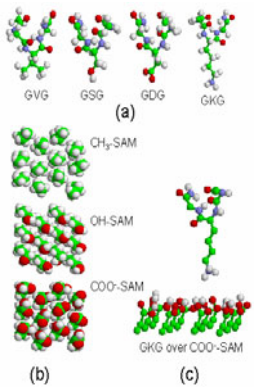

Fig.1 Molecular models of four peptides (a), three SAM surface (b), and a typical set-up for DFT/SCRF calculations (c).

Results / Discussion: The ΔG_{ads} vs. *SSD* relationships determined from the DFT/SCRF calculations predict five distinctively different types of characteristic behavior based on the chemical nature of the functional groups involved. These characteristics can be generalized as follows. (1) A nonpolar peptide residue will adsorb tightly to a nonpolar surface due to the hydrophobic effects. (2) A charged peptide residue will experience long-range attraction to an oppositely-charged surface and then encounter a desolvation energy barrier at a surface separation distance corresponding to 1-2 water-shell layers of thickness, which it must overcome in order to form a stable salt bridge with functional groups on the surface. (3) When a charged peptide residue approaches a surface with same-charged functional groups, it will experience long-range repulsion that substantially increases in intensity as the peptide approaches within 1-2 solvation layers of the surface. (4) A neutral hydrophilic peptide residue approaching a neutral hydrophilic surface will experience negligible long-range effects and then encounter a steadily increasing desolvation energy barrier at a separation distance corresponding to 1-2 water-shell layers of thickness. (5) Other residue/surface systems comprised of mixed types of hydrophilic, charged, and neutral hydrophilic functional groups show similar behavior to the neutral hydrophilic system. Comparisons of the DFT/SCRF calculations with C19 combined with the four different implicit solvation methods show that each type of implicit solvation method predicts substantially different ΔG_{ads} vs. *SSD* behavior. In general, the RDIE and EEF1 methods did the poorest job accounting for solvation effects and effectively represented peptide/surface interactions to be similar to 'dampened vacuum' conditions. ASP and ACE, on the other hand, were able to represent solvation effects very effectively for many of the systems, with the ACE methods providing the closest agreement with DFT/SCRF calculations overall. This being said, ACE still showed functional groups combinations where it predicted solvation effects that were substantially different than those predicted by SCRF theory. In particular, ACE tended to over-dampen electrostatic interactions and over-estimate hydrophobic effects. The latter condition indicating that a value of the adjustable surface tension parameter (σ) much lower than σ=15 should be used with this implicit solvation model for the calculation of peptide interactions with functionalized surfaces.

Conclusions: Performance comparison between empirical force field-based implicit solvent models and DFT/SCRF calculations has been carried out by obtaining the energy-distance relationship associated with the process of a protein residue approaching a material surface in aqueous solution. Results indicate several areas of discrepancy as well as agreement between the two methods. These comparisons provide a basis for selecting the best implicit solvent model for use with empirical force field calculations and for subsequent adjustment of its parameters to increase its ability to accurately represent protein-surface interactions.

References: 1) Martern et al. *J. Phys. Chem.* 100: 11775 (1996). 2) Brooks et al. *J. Comput. Chem.* 4: 187 (1983). 3) Scheafer & Karplus, *J. Phys. Chem.* 100:1578 (1996). 4) Wesson & Eisenberg, *Protein Sci*. 1:227 (1992). 5) Lazaridis & Karplus, *Proteins*, 35:133(1999). 6) Schaefer et al. *Theor. Chem. Acc.* 101: 194 (1999).

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