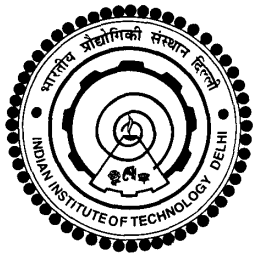
USING COMPUTER SIMULATIONS TO UNDERSTAND THE ROLE OF WATER AS A SOLVENT IN BIOMOLECULAR SYSTEMS

DIVYA NAYAR



DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY DELHI

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USING COMPUTER SIMULATIONS TO UNDERSTAND THE ROLE OF WATER AS A SOLVENT IN BIOMOLECULAR SYSTEMS

by

DIVYA NAYAR

DEPARTMENT OF CHEMISTRY

Submitted

in fulfillment of the requirements of the degree of

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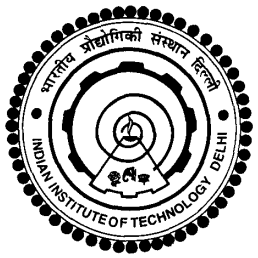
to the



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To My Parents

Certificate

This is to certify that the thesis titled **"USING COMPUTER SIMULATIONS TO UNDERSTAND THE ROLE OF WATER AS A SOLVENT IN BIOMOLECULAR SYSTEMS"** is being submitted by **Ms. Divya Nayar** to the Department of Chemistry, Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy**. This thesis is a record of bona-fide research work carried out by her under my guidance and supervision. In my opinion, the thesis has reached the standards fulfilling the requirements of the regulations relating to the degree.

The results contained in this thesis have not been submitted to any other University or Institute for the award of any degree or diploma.

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Abstract

This thesis examines the hydration behaviour of water in the neighbourhood of biomolecular solutes in terms of its role in shaping the secondary structure preferences of peptides using molecular dynamics simulations. As a first step towards understanding the hydration behaviour, the relationship between structural order, energy and thermodynamic anomalies is examined for rigid-body water models in bulk. The commonly used solvent models of water are shown to have very different energetic bias towards tetrahedrality, although they show similar relationships between structural order and the density anomaly. We then examine the structural estimators of entropy, commonly used for studying biomolecular solvation and show that they can be applied to examine solvation thermodynamics of other nanoscale solutes, such as alkylthiol passivated gold nanoparticle. The hydration shell structure and energetics of rigid-body water models are examined in the neighbourhood of simple, structure-less polar (Na^+, Cl^-) and non-polar (Ar) solutes as well as complex biomolecular solute like 16-residue β-hairpin fragment of 2GB1 protein with CHARMM22 force-field. Despite qualitative differences in bulk properties, the water models show only quantitative differences in hydration shell behaviour around the folded peptide, due to parameterization of force-fields under conditions when the folded, native structure is thermodynamically stable. Therefore, the hydration shell structure and conformational preferences of the peptide are compared in the unfolded ensemble of the peptide in different rigid body water models. The conformational preferences of unfolded ensemble of peptide show sequence-dependent sensitivity to choice of water model. To understand the effect of tuning intermolecular interactions in water on the free energy landscape of peptides, we then perform replica exchange molecular dynamics simulations of alanine di- and pentapeptide in rigid-body water models and hybrid solvent models. This study highlights the significance of interplay between intrapeptide, peptide-solvent and solvent-solvent hydrogen bonding in determining secondary structure preferences of peptides and demonstrates that adequate representation of such interactions is essential while modeling secondary structure of peptides.

Permissions

Permissions have been taken from the respective journals for the publications related to work presented in this thesis.

List of Publications Related to Work Presented in this Thesis as on Date of Submission of Thesis

1. **Divya Nayar**, Manish Agarwal and Charusita Chakravarty, "Comparison of Tetrahedral Order, Liquid State Anomalies, and Hydration Behavior of mTIP3P and TIP4P Water Models", *J. Chem. Theory Comput.* **7**, 3354-3367 (2011).

2. B. Shadrack Jabes, **Divya Nayar**, Debdas Dhabal, Valeria Molinero and Charusita Chakravarty, "Water and other Tetrahedral Liquids: Order, Anomalies and Solvation", *J. Phys.: Condens. Matter.* **24**, 284116 (2012).

3. **Divya Nayar**, Hari Om Sharanam Yadav, B. Shadrack Jabes and Charusita Chakravarty, "Relating Structure, Entropy and Energy of Solvation of Passivated Metal Nanoparticles", *J. Phys. Chem. B.* **116**, 13124-13132 (2012).

4. **Divya Nayar** and Charusita Chakravarty, "Water and Water-like Liquids: Relationships between Structure, Entropy and Mobility", *Phys. Chem. Chem. Phys.*, **15**, 14162-14177 (2013).

5. **Divya Nayar** and Charusita Chakravarty, "Sensitivity of Local Hydration Behaviour and Conformational Preferences of Peptides to Choice of Water Model", *Phys. Chem. Chem. Phys.*, **16**, 10199-10213 (2014).

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