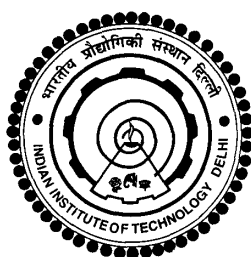


USING COMPUTER SIMULATIONS TO UNDERSTAND THE ROLE OF WATER AS A SOLVENT IN BIOMOLECULAR SYSTEMS

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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY DELHI
JUNE 2015

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by

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DEPARTMENT OF CHEMISTRY

Submitted

in fulfillment of the requirements of the degree of

Doctor of Philosophy

to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI

JUNE 2015

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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ACKNOWLEDGMENTS

I would like to express my heartfelt gratitude to all the people who have contributed to this thesis with their constant encouragement and support.

First and foremost, I would like to extend my earnest gratitude and regards to my supervisor, Prof. Charusita Chakravarty who has been an exceptional mentor, outstanding teacher, and a great advisor. I want to thank her for all the unconditional support, selfless efforts, consistent help and valuable guidance that she has extended, in order to make this thesis possible. For me, she is an epitome of perfection, hard-work, determination and optimism; and her qualities have inspired me to grow as a researcher as well as a person. Her constant encouragement and motivation have shown me new perspectives of life that have enabled me take right decisions and realize my objectives. I am grateful to her for patiently guiding me, for being so compassionate and for always standing beside me through the tough times. I thank her for her consistent efforts to bring out the best in me and for always wishing the best for me. I feel blessed and honored to be her student.

My special thanks to Prof. Ramakrishna Ramaswamy for giving useful suggestions and ideas during the Saturday meetings at JNU, New Delhi. I thank my Research Committee members- Prof. A. K. Ganguli (Department of Chemistry), Dr. Shashank Deep (Department of Chemistry), Prof. Ratnamala Chatterjee (Department of Physics) for their timely evaluation, valuable suggestions and for asking interesting questions during my Comprehensive and Synopsis viva which made me think beyond my work and helped me improve. A special thanks to Dr. Pramit K. Chowdhury (Department of Chemistry) for useful discussions, wonderful suggestions and interesting insights into the research work. His course work and valuable notes have helped me a lot in carrying the work forward and in writing this thesis. I extend my special gratitude to Prof. Debasisa Mohanty (NII, New Delhi) for being the external expert of my research committee and for giving useful suggestions regarding work. I thank the faculty members of Physics and Chemistry Departments

and Computer Service Center, whose course work helped me a lot in building my concepts and helped me in laying the foundation of my research work. I thank DRC Chairmen, Prof. A. K. Singh and Prof. A. Ramanan and all the other faculty members of the Department of Chemistry for their help and support during the years of my Ph.D. My special thanks to Prof. Pragya Jain (CSC, IIT Delhi) for always being ready to extend her help in solving issues regarding VM and the cluster at CSC.

I would like to thank Computer Services Center at IIT Delhi for computational support and facilities, without which the work of this thesis would not have been possible. I am grateful to IIT Delhi Library for book and journals, which have formed the backbone of this thesis. I thank the Chemistry Department office staff and all the other staff members of IIT Delhi for their help and support in the administrative work involved during Ph.D. I thank Council of Scientific and Industrial Research (CSIR, New Delhi) for junior and senior research fellowship. I thank Department of Science and Technology (DST, New Delhi) for providing funds to attend the international conference.

A special thanks to Prof. Valeria Molinero, The University of Utah and Prof. Sanjoy Bandyopadhyay, IIT Kharagpur for their constant encouragement and guidance in research work. I would also like to acknowledge the efforts and guidance of my teachers at St. Stephen's College, Chemistry Department of Delhi University and Convent of Jesus and Mary School, New Delhi who enlightened me to the path of scientific journey. A special thanks to Dr. S. V. Eswaran (St. Stephen's College) who exposed me to the world of scientific research and helped me recognize my potential. His lectures and afternoon discussions on philosophical insights into science, fascinated me and motivated me to take up research as career. I would also like to thank the faculty with whom I carried out my summer research projects during graduation and post-graduation, for their guidance that helped me to choose this field of research.

The contribution of my fellow lab mates in my Ph.D. is precious and treasured. I begin by thanking Dr. Manish Agarwal, whose help and guidance, specially with the computing skills and techniques, in my nascent years of Ph.D. helped me to embark on with my research work. Thanks to Dr. Ruchi Sharma for her beautifully

handwritten notes and systematic presentations. My special thanks to two colleagues and friends- Murari Singh and Shadrack Jabes- who made the lab environment amicable and dynamic. Murari's philosophical theories on life, his cheerful and entertaining nature made work enjoyable. Shadrack's inspirational Bible stories, music skills and his scientific ways of fixing things in lab, kept the work environment alive and motivated. My other lab members also contributed tremendously towards my thesis. I thank Hari Om for his motivational lectures on importance of seeking a good job and earning money in life; Debdas, for being a sincere and hard-working junior, who selflessly helped me in various tasks related to work; Saurav, for keeping me updated about new happenings in the campus and elsewhere; Madhulika, for being a sweet and helpful junior who gave me good company during the lunch times and during conferences; Gourav, for the discussions on politics and common man. I thank all my fellow lab mates for all the timely discussions we have had regarding work, that helped me to foster my work. I also thank the summer students and M.Sc students- Ambuj and Sohona for instilling the enthusiasm and excitement in research work.

Above all, I thank my family members for being my strength during Ph.D. I am grateful to my paternal grandparents for their good wishes and blessings which have helped me realize my goals. My heartfelt gratitude to my late maternal grandmother, who always encouraged and motivated me towards making education my strength. My heartiest thanks and regards to my parents, whose sacrifices, support, blessings and guidance have made this thesis possible. I am thankful to them for believing in me and for encouraging me to believe in myself. They have been my pillars of strength who have always stood by me in all my endeavours. I am grateful to my sister, for always instilling in me the confidence to fulfill my aspirations. She has contributed to this thesis by inspiring me with her analytical reasoning and creativity. A special thanks to my three year old nephew- Parth, whose inquisitive young mind and countless questions have compelled me to re-think about scientific facts!

I am thankful to Almighty for making this thesis possible !

Divya Nayar

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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