COMPUTER SIMULATIONS OF FREE ENERGY LANDSCAPES OF PEPTIDES, THEIR HYDRATION BEHAVIOR AND METAL SURFACE DEACTIVATION

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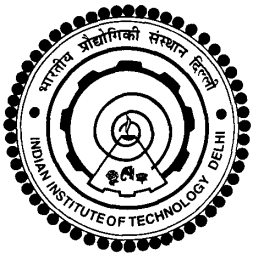

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY DELHI

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COMPUTER SIMULATIONS OF FREE ENERGY LANDSCAPES OF PEPTIDES, THEIR HYDRATION BEHAVIOR AND METAL SURFACE DEACTIVATION

by

MADHULIKA GUPTA

DEPARTMENT OF CHEMISTRY

Submitted

in fulfillment of the requirements of the degree of Doctor of Philosophy

to the

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Dedicated To My Parents,
Nani, (Late) Nanaji and
(Late) Prof. Charusita Chakravarty

Certificate

This is to certify that the thesis titled **"COMPUTER SIMULATIONS OF FREE ENERGY LANDSCAPES OF PEPTIDES, THEIR HYDRATION BEHAVIOR AND METAL SURFACE DEACTIVATION"** is being submitted by **Ms. Madhulika Gupta** 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 the supervision of (Late) Prof. Charusita Chakravarty from 2 January, 2012 to 29 March, 2016 and subsequently under our guidance. In our 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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Madhulika Gupta Date

Abstract

This thesis employs computer simulations to examine conformational preferences of peptides along the folding free energy landscape (FEL), role of hydration waters in mediating protein-glass transition and folding-unfolding equilibria, and deactivation of catalyst surfaces by biogenic impurities in fermentation derived feedstocks. As a first step to achieve this goal, we assess how small quantitative differences in different water models translate into significant dependence of conformational FEL for 20-residue, α-helical Trp-cage, on the choice of water models. The same set of water models generate qualitatively different secondary structure preferences for the unfolded peptide with a sequence-dependent response to the choice of water model. This study highlights the importance of adequate representation of peptide-water interactions to obtain better predictive values of biomolecular force fields, especially for the unfolded states. The effect of water models on the solvent-driven, protein-glass transition for Trp-cage is also examined. The correlated protein-water dynamics is unaffected by the choice of model, while the activation of methyl dynamics shows considerable sensitivity. The alterations induced in the folding pathway of 16-residue trpzips obtained by progressive substitution of hydrophobic core residues have been explored by performing replica exchange molecular dynamics simulations. The role of water in mediating protein-unfolding with sequential changes in hydration behaviour for encompassing set of metastable states with partially unfolded structures is outlined. Mutations modify packing of peptide backbone to adjust the changes in side chain volume, resulting in reshaping of the FEL for mutated peptides. The differential hydration behavior among the strand and turn regions of trpzips owing to their motional heterogeneity regulates the unfolding process. Finally, an approach towards understanding the physicochemical principles governing interactions and poisoning of metal surfaces by amino acids with varying side chain specificity is made by using steered molecular dynamics simulations. A bimetallic design of catalyst surface is examined to mitigate surface poisoning.

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

1. **M. Gupta**, D. Nayar, C. Chakravarty and S. Bandyopadhyay, Comparison of Hydration Behaviour and Conformational Preferences of the Trp-cage Miniprotein in Different Rigid-Body Water Models, *Phys. Chem. Chem. Phys.*, **18**, 32796 (2016).

2. **M. Gupta**, C. Chakravarty and S. Bandyopadhyay, Sensitivity of Protein Glass Transition to the Choice of Water Model, *J. Chem. Theory Comput.*, **12**, 5643 (2016).

3. **M. Gupta**, T. S. Khan, S. Gupta, Md. I. Alam, M. Agarwal, M. A. Haider, Non-Bonding and Bonding Interactions of Biogenic Impurities with the Metal Catalyst and the Design of Bi-Metallic Alloys, *J. Catal.*, **352**, 542 (2017).

4. **M. Gupta**, P. Khatua, C. Chakravarty and S. Bandyopadhyay, The Sensitivity of Folding Free Energy Landscapes of Trpzips to Mutations in the Hydrophobic Core, *Phys. Chem. Chem. Phys.*, **19**, 22813 (2017).

5. **M. Gupta**, P. Khatua, C. Chakravarty and S. Bandyopadhyay, Hydration Behaviour along the Folding Pathway for Trpzip4, Trpzip5 and Trpzip6, *J. Phys. Chem. B*, (2018).

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सार

इस थीसिस कंप्यूटर के सिमुलेशन को कन्सर संबंधी वरीयताओं की जांच करने के लिए कार्यरत हैं तह मुक्त ऊर्जा परिदृश्य (एफईएल), जलयोजन जल की भूमिका के साथ पेप्टाइड्स प्रोटीन कांच संक्रमण और तह-प्रबुद्ध संतुलन, और निष्क्रियकरण में मध्यस्थता में किण्वन व्युत्पन्न फीडस्टॉक में बायोजेनिक अशुद्धियों द्वारा उत्प्रेरक सतहों की। इस लक्ष्य को प्राप्त करने के पहले चरण के रूप में, हम आकलन करते हैं कि इसमें कितने छोटे मात्रात्मक अंतर हैं विभिन्न जल मॉडल, गठनात्मक एफ ए एल के महत्वपूर्ण निर्भरता में अनुवाद करते हैं पानी के मॉडल की पसंद पर 20-अवशेष, α- पेचदार ट्रिप - पिंजरे के लिए। का एक ही सेट पानी के मॉडल के लिए गुणात्मक रूप से भिन्न माध्यमिक संरचना प्राथमिकताएं उत्पन्न होती हैं पानी मॉडल की पसंद के अनुक्रम-आश्रित प्रतिक्रिया के साथ पेप्टाइड सामने आया। इस अध्ययन में पेप्टाइड-पानी के पर्याप्त प्रतिनिधित्व के महत्व पर प्रकाश डाला गया है बायोमोलेक्युलर फोर्स फील्ड्स के बेहतर भविष्य कहां प्राप्त करने के लिए इंटरैक्शन खुला राज्यों के लिए विलायक-संचालित, प्रोटेक्शनलास पर पानी के मॉडल का प्रभाव ट्रिप-पिंजरे के लिए संक्रमण की जांच भी की जाती है। सहसंबद्ध प्रोटीन-पानी की गतिशीलता मॉडल की पसंद से अप्रभावित है, जबकि मिथाइल गतिशीलता का सक्रियण काफी संवेदनशीलता दिखाती है तह के मार्ग में प्रेरित परिवर्तन हाइड्रोफोबिक कोर अवशेषों के प्रगतिशील प्रतिस्थापन द्वारा प्राप्त 16-अवशेषों ट्रिपज़िप प्रतिकृति विनिमय आणविक गतिशीलता सिमुलेशन के प्रदर्शन से पता लगाया गया है। जलयोजन में अनुक्रमिक परिवर्तन के साथ प्रोटीन-खुलासा में मध्यस्थता में पानी की भूमिका आंशिक रूप से सामने आने वाले महानतम राज्यों के सेट को शामिल करने के लिए व्यवहार संरचनाओं को रेखांकित किया गया है। उत्परिवर्तन समायोजित करने के लिए पेप्टाइड रीढ़ की पैकिंग को संशोधित करता है साइड चेन वॉल्यूम में परिवर्तन, जिसके परिणामस्वरूप उत्परिवर्तित के लिए एफईएल के पुनर्निर्धारण में हुई पेप्टाइड्स। किनारा और मोड़ के क्षेत्रों में अंतर हाइड्रेशन व्यवहार उनकी गति विविधता के कारण ट्रिपज़िप खुलासा प्रक्रिया को नियंत्रित करता है। आखिरकार, भौगोलिक रासायनिक सिद्धांतों को समझने की दिशा में एक दृष्टिकोण विभिन्न साइड चेन के साथ अमीनो एसिड द्वारा धातु की सतहों की बातचीत और विषाक्तता विशिष्टता को स्टीयरेड आणविक गतिशीलता सिमुलेशन का उपयोग करके बनाया गया है एक बाईमेटेलिक सतह के विषाक्तता को कम करने के लिए उत्प्रेरक की सतह के डिजाइन की जांच की जाती है |

Contents

List of Figures

List of Tables