INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: The Dual Role of Choline-*O*-sulfate on Chemical Denaturation of Proteins and Amyloid Aggregation: A Computational Study

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SHORT ABSTRACT

This thesis represents the molecule choline-O-sulfate as a protecting osmolyte in the protein folding-unfolding process as well as a potent inhibitor in the field of peptide aggregation. The thesis is divided into seven chapters. **Chapter 1** of the thesis includes a review of related experimental and theoretical works that exist in the literature together with the basic techniques of MD simulations. In **Chapter 2**, we have studied the synergistic behavior of urea-COS mixture through classical molecular dynamics simulation. Here we have studied all possible interactions between urea and COS present in a mixture to find out the mechanism of the counteraction of urea by COS against urea-induced denaturation of the protein. **Chapter 3** deals with the direct application of COS as a protecting osmolyte in the protein folding-unfolding process. This chapter has been divided into two parts, **Part A** and **Part B**. **Chapter 3A** describes how COS nullifies the deleterious effects of urea on a 15 residue modeled peptide named S-peptide through classical molecular dynamics simulation. **Chapter 3B** includes the findings on the counteracting ability of COS against urea on a small globular protein called Trp-cage by an enhanced sampling method called Replica Exchange Molecular Dynamics (REMD) simulation. In the next chapter i.e. **Chapter 4**, we have discussed the unfolding of the terminal helices of the λ-repressor protein by an unconventional denaturant dodine and its stability in presence of COS. In **Chapter 5**, we have reported our research work on the inhibitory effects of COS in the aggregation of human islet amyloid polypeptide, responsible for Type-II diabetes mellitus (T2Dm). In **Chapter 6**, we have presented COS as a potent inhibitor in the self-association of $A\beta_{16-22}$ peptide, associated with Alzheimer's disease. In the last chapter i.e., **Chapter 7**, we have summarized our overall findings to bring a concrete conclusion portraying COS as an efficient osmolyte as well as an inhibitor. Successful application of COS on two different kinds of proteins (cellular protein S-peptide and globular protein Trp-cage) against the chemical denaturant urea would help to draw attention to the wider approach of COS as a counteracting osmolyte in protein misfolding. This naturally occurring molecule is not only able to withstand against the traditional chemical denaturant urea, its counteracting ability is quite appreciable against the surfactant denaturant dodine. Moreover, this non-toxic molecule can inhibit the fibrillation of hIAPP and $A\beta_{16-22}$ peptides, associated with Type-II diabetes mellitus and Alzheimers disease, respectively, which can be attributed to the therapeutic approach to these neurodegenerative diseases and molecular drug discovery. In short, this dissertation can provide a new insight in the field of biochemistry related to protein dysfunction.