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Theoretical Study on the Influence of Solvent on Subtilisin Catalysis YIMING ZHANG, Rensselaer Polytechnic Institute, LU YANG, Rensselaer Polytechnic Institute, JONATHAN DORDICK, Rensselaer Polytechnic Institute, SHEKHAR GARDE, Rensselaer Polytechnic Institute, SAROJ NAYAK, Rensselaer Polytechnic Institute — Using a hybrid quantum mechanical and molecular mechanical (QM/MM) approach we have studied subtilisin catalysis in water and tetrahydrofuran (THF). Extensive classical molecular dynamics simulations have been carried out in order to obtain the solvent structure around the protein, while hybrid QM/MM method is used to provide the reaction energy profile for the enzymatic reaction. The reaction energy barrier for the formation of the enzyme's tetrahedral intermediate in water is found to be about 7 kcal/mol lower than formation of the tetrahedral intermediate in THF. This result is in good agreement with experimental data where the reactivity of subtilisin is up to four orders of magnitude lower in THF than in water. The lower reaction barrier in water is related to the enhanced stabilization of the enzyme's transition state (TS) in water through hydrogen bonding between solvent water molecules and the TS complex. In addition, we find that the role of Asp32 in stabilizing the tetrahedral intermediate state abates in THF.

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