CAN MOLECULAR DYNAMICS AND QM/MM NBO SOLVE THE PENICILLIN BINDING PROTEIN PROTONATION PUZZLE?

Jacqueline C. Hargis, Justin K. White, & H. Lee Woodcock

Department of Chemistry, University of South Florida, Tampa, Florida 33620, United States

Benzylpenicillin, a member of the β-lactam antibiotic class, has been widely used to combat bacterial infections since 1947. The general mechanism is well known: a serine protease enzyme (i.e. DD-peptidase) hydrolyzes the lactam ring of the antibiotic (acylation & deacylation), effectively preventing biosynthesis of the bacterial cell wall. Despite this overall mechanistic understanding, many details of binding and catalysis are unclear. There is ongoing debate about active site protonation states and the role of general acids / bases in the reaction. An investigation of the pre-acylated *Streptomyces* R61 active site with bound benzylpenicillin was carried out. We examined the critical interactions necessary to maximize the stability of benzylpenicillin and identify the protonation state that most effectively exploits these favorable interactions. We carried out this study using a systematic approach that varied the protonation states of active site residues. The combination of MD simulations followed by QM/MM minimization and NBO has lead to a novel approach for identifying protonation states.