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The Molecular Mechanical Model of DD-Peptidase

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In order to establish the structural requirements for designing new β-lactam antibiotics it is necessary to build the molecular model of a penicillin binding protein. D-alanyl-D-alanine carboxypeptidase/transpeptidase (DD-peptidase) is a good model for PBPs. The X-ray crystallographic structure of DD-peptidase has been reported at the 1.6Å resolution. Based on the heavy atom coordinates, the molecular model of 5,952 atoms, including all hydrogen atoms explicitly, is built. The model has one disulfide linkage of Cys 291-Cys 344 and consists of 13 α-helices and 15 β-strands. By evaluating solvent accessibility to carboxyl oxygens, all Glu and Asp are determined to be in the carboxylate form. By examining hydrogen bonding possibility and solvent accessibility to nitrogen atoms in the hetero ring, the protonation state of histidines is determined. His 147, His 200, and His 209 are assigned with the ε-protonated form (HSE) and the rest are δ-protonated histidines (HSD). The X-ray crystallographic structure reports that 16 residues assume doubly definable conformations. Based on our first stage molecular model, the most realistic conformation is being determined by using constrained minimization and molecular dynamics techniques. The current work is the first step toward constructing the database for de novo antibiotics lead design through the free energy simulations and subsequent component analyses.