

## **426n Combined Simulation Approach of Atomistic and Continuum Models for the Thermodynamics of Lysozyme Crystals**

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We have studied the thermodynamic properties of protein crystals using a novel simulation method combining atomistic Monte Carlo simulation to calculate van der Waals interactions and the boundary element method to solve the Poisson-Boltzmann equation for the electrostatic interactions. Attention is focused on hen egg white lysozyme, for which thermodynamic properties are known experimentally. For computational simplicity, we treat the protein as a rigid body, using the crystallographic coordinates of all nonhydrogen atoms of the protein to describe the detailed shape. NVT Monte Carlo simulations are carried out for tetragonal and orthorhombic lysozyme crystals containing 16 protein molecules in order to obtain the van der Waals energy, with an implicit solvation effect incorporated as well. The electrostatic energy is calculated separately by solving the Poisson-Boltzmann equation using the boundary element method. For crystal phases, an optimally linearized Poisson-Boltzmann equation is used to include the Donnan equilibrium of the salt ions. The Helmholtz energy is obtained by adding the electrostatic energy as a perturbation to the van der Waals contribution calculated from expanded ensemble Monte Carlo simulations. Reasonable agreement with experiment is found for the energy of the tetragonal structure, with some variation among different sets of PDB crystallographic coordinates. Using the force field parameters that had previously been tuned for the solution properties, the deviation from experiment is less than 20%. The entropy of the tetragonal crystal is underestimated by about 10% indicating that the rigid protein model results in crystal structures that may be too tight, and may also due to the neglect of the vibrational entropy gain. The predictions of the properties of the orthorhombic crystal are poor, probably due to differences in solvation behavior and the limitations of the present force field.