

**PATHWAYS AND PROTONATION STATES IN THE MECHANISM
OF PROTEIN TYROSINE PHOSPHATASE: A STUDY USING
COMBINED MACROSCOPIC AND QUANTUM-MECHANICAL
MODELS**

DILIPKUMAR ASTHAGIRI¹, VALERIE DILLET¹, TIQING LIU¹, LOUIS
NOODLEMAN¹, ROBERT L VAN ETTEN² and DONALD BASHFORD¹

¹ Scripps Research Institute, Department of Molecular Biology, La Jolla,
CA 93027, USA, ² Purdue University, Biochemistry & Molecular Biology
Program, West Lafayette, IN 47907-2063, USA

We have used a combination of the MEAD (macroscopic electrostatics with atomic detail) model and DFT methods to investigate states of protonation and the catalytic mechanism in the PTPases (protein tyrosine phosphatases). MEAD calculations have showed how an arrangement of backbone dipoles and other features stabilizes an unusual combination of protonation states (deprotonated Cys, protonated Asp) needed for catalysis. Combining this electrostatic model with explicit quantum mechanical (DFT) modeling of the substrate and crucial active-site residues, we have calculated reaction profiles for both the protein phosphorylation step and the enzyme dephosphorylation step. We address several mechanistic questions including protonation states in the first step, associative versus dissociative pathways in the both steps, proton transfer as an initiating event in the second step, and activated versus direct attack by water in the second step.