MP2 Calculations of Interaction Energies Between Acetaminophen and Acetaminophen Analogues in Aryl Sulfotransferase

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Paracetamol, or acetaminophen, is a commonly used analgesic and antipyretic. There are three major ways that acetaminophen can be metabolized in the liver; glucuronidation, sulfation, and N-hydroxylation and GSH conjugation. The nontoxic products from each pathway are excreted by the kidneys. Cresols such as *p*-cresol, *o*-cresol, and *m*-cresol can compete with acetaminophen for metabolism. They are found in various foods, beverages, and in the combustion of certain materials. We have applied correlated quantum mechanical methods, such as MP2, and DFT methods to study the interaction of acetaminophen and these cresol analogues with the active site of aryl sulfotransferase, which is involved in the sulfation pathway. Docking followed by optimization with BHandHLYP was used to find the structures of the ligand-protein complexes assuming a static active site. Interaction energy calculations were then performed between the ligands and each of the amino acids in the sulfotransferase enzyme active site. From these calculations, we can determine the strength of the ligand-protein binding. In addition, optimizations were also performed to allow flexibility of the different amino acid residues involved in the active site and interaction energies were calculated for these complexes as well. Interaction energies were calculated using both MP2 and SVWN with a basis set of 6-311+g*. Each of the amino acids were adjusted to be in their state found at biological pH. From these calculations, we can compare the total interaction energies obtained for the cresol analogues in the active site, with those for acetaminophen. From this, we can offer predictions as to how competitive the cresol analogues are with acetaminophen for metabolism.

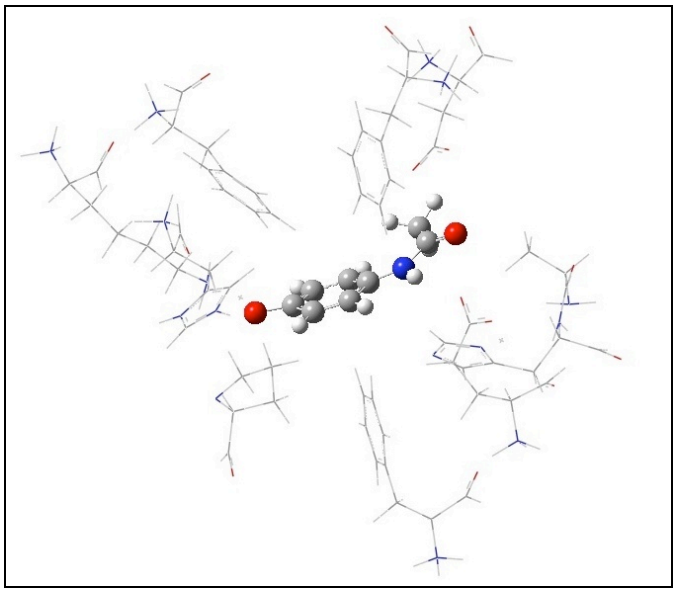

Figure 1. Optimized structure of acetaminophen (ball-and-bond) in the aryl sulfotransferase active site (wireframe).