MP2 Interaction Energies between Acetaminophen and Acetaminophen Analogues and the Glucosyltransferase Active Site

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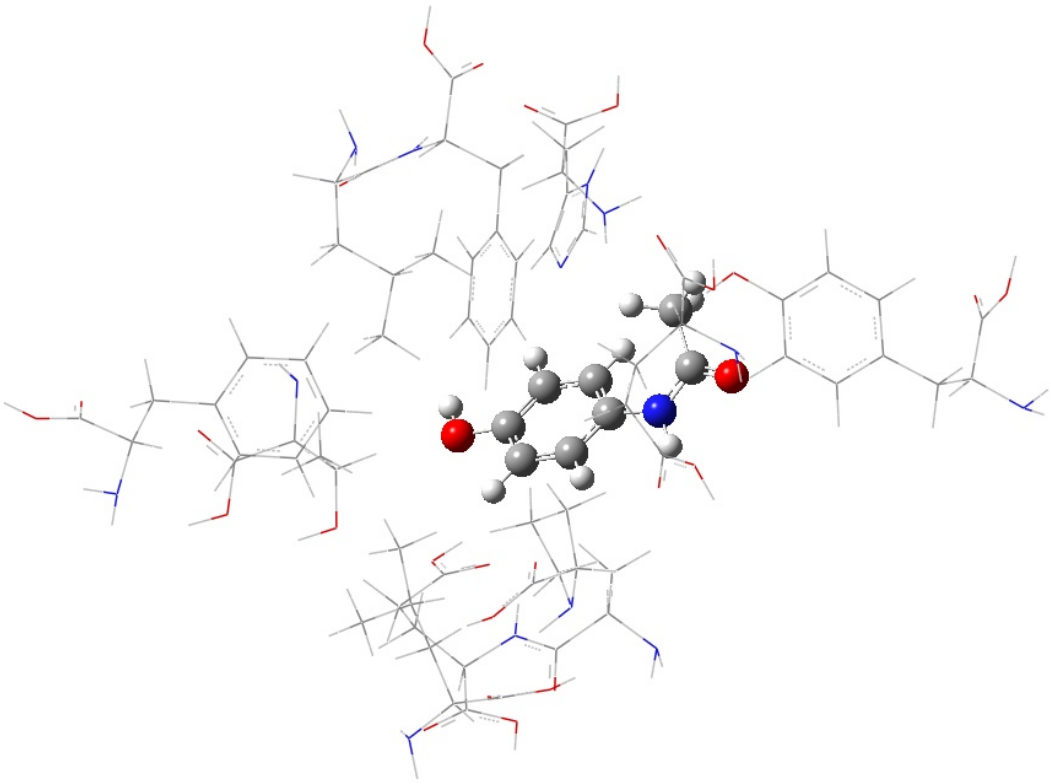
Paracetamol, or acetaminophen, is a commonly used analgesic and antipyretic. Cresols such as *p*-cresol, *o*-cresol, and *m*-cresol can compete with acetaminophen for metabolism via several pathways, including via glucoronodation by glucoronyltransferase. We have applied the MP2 method to study the interaction of acetaminophen and these cresol analogues with the active site of glucosyltransferase. While a crystal structure is not available for glucoronyltransferase, there is evidence that the active site of glucosyltransferase is highly homologous to that of glucoronyltransferase. Docking and BHandHLYP/6-31G optimization were used to find the structures of the ligand-protein complexes assuming a static active site. Interaction energies between the ligands and each of the amino acids in the active site were calculated using MP2 with a basis set of 6-311+g*. Further optimizations were then performed to allow flexibility of the amino acid residue side-chains in the active site and interaction energies were calculated for these complexes as well. *p*-cresol is shown to compete with acetaminophen for this metabolic pathway, in agreement with experiment.



(Acetaminophen docked in the glucosyltransferase active site)