MP2 and DFT analysis of the ligand selectivity of a sulfotransferase enzyme part 1: SULT 1A3

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We have studied the substrate selectivity of the sulfotransferase enzyme (SULT1A3) by identifying important protein-ligand interactions in the active-site through electronic structure calculations. The sulfotransferase enzymes (SULTs) catalyze the addition of a sulfate group to a variety of small molecules, including neurotransmitters and xenobiotics. This reaction can activate or deactivate bio-active molecules or change their pharmacokinetic behavior. A variety of ligands analogous to known substrates of the SULT were chosen for study. Docking and M062X/6-31G optimization of the ligands were used to find the structures of the ligand-protein complexes assuming a static active-site. Interaction energies between the ligands and the amino-acids of the active-site were calculated using MP2 and M062X with 6-311+g*; these energies can be used to determine the thermodynamic stability of the ligand in the active site. The addition of the sulfuryl group to the ligand depends on deprotonation of a phenol group on the ligand. Thus, pKa values were calculated for each of the ligands to determine the ease of deprotonation. Interaction energies and pKa values indicate different selectivity and comparison with experimental values is being used to determine which approach is most accurate. All calculations were performed with and without implicit solvation and with a rigid and a flexible active site.

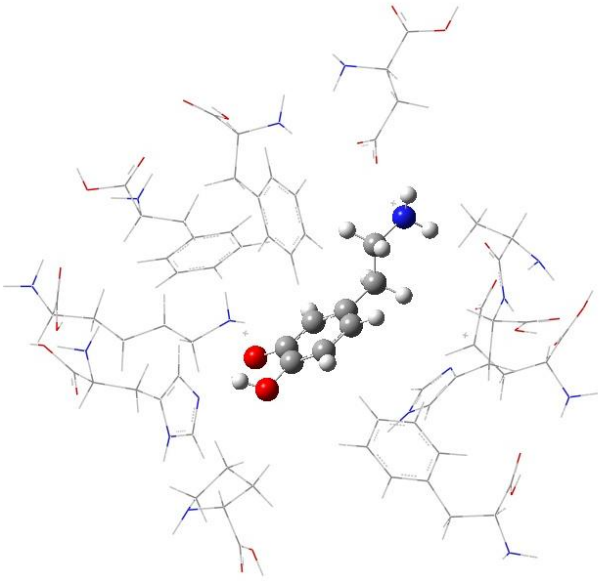

Figure 1: dopamine docked in the sulfotransferase active site