

Thermodynamic and Kinetic Interactions of Ligands in the SULT1A1 Active Site

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We have studied the substrate selectivity of the sulfotransferase enzyme (SULT1A1) 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. M062X/6-31G optimization of the ligands was used to find the structures of the ligand-protein complexes in three ways: assuming a static active-site, a static active site with implicit solvent, and a relaxed active site with implicit solvent. 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 sulfonyl group to the ligand depends on deprotonation of a phenol group on the ligand. Thus, the activation energies for proton extraction from the ligand to the histidine residue were calculated.

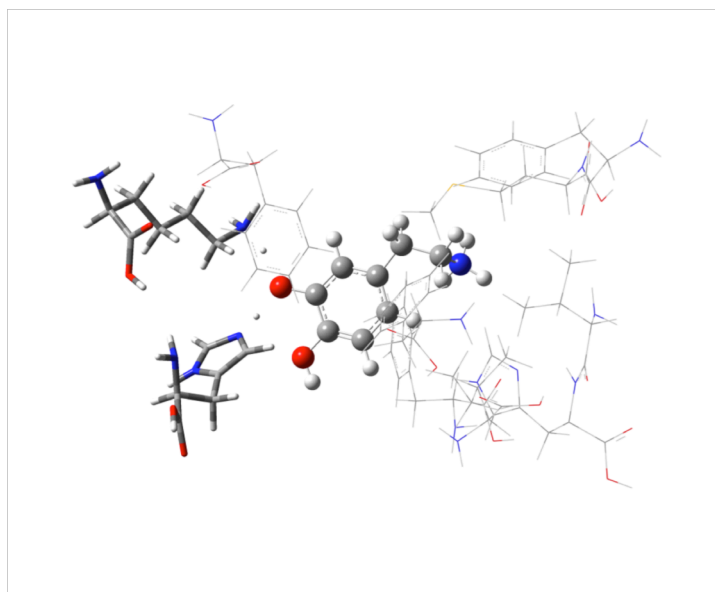


Figure 1. Dopamine Docked in SULT1A1 enzyme.