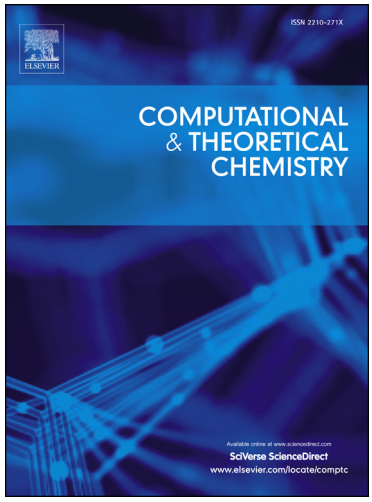

DFT and MP2 study of the effects of point mutations on the binding of ligands within the SULT1A3 active site

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DFT and MP2 study of the effects of point mutations on the binding of ligands within the SULT1A3 active site

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Abstract
Sulfotransferases (SULTs) are important in the metabolism and regulation of xenobiotics and endogenous substrates, such as neurotransmitters. In this study, we apply a previously validated model chemistry [D.J. Bigler, *et al.* Comp. Theor. Chem. 1051, 79 (2014)] to study the role of specific active site amino acid residues in the selectivity of SULT1A3 for particular ligands. Experimental work [L.A. Brix, *et al*. Biochemistry 38, 10474 (1999) and M.-C. Liu, *et al.* Journal of Biological Chemistry. 275, 13460 (2000)] has verified the importance of two amino acid residues in the binding of ligands to this active site (E146 and D86); the current work provides a molecular-level explanation for the observed results and then offers further interpretation of specific interactions important to ligand binding. A suite of ligands were optimized in three mutant SULT1A3 active sites using M062X/6-31G with relaxed amino acid side chains and implicit solvation. M062X/6-311+G* and MP2/6-311+G* were used to calculate counterpoise-corrected interaction energies between the ligands and the mutant active site residues. These results were found to agree well with the experimental site-directed mutagenesis studies of SULT1A3.

1. Introduction

In recent work, we investigated electronic interaction energies of dopamine, seven dopamine analogues, and resveratrol within the SULT1A3 active site with three different model chemistries: *in vacuo* optimization of ligands in a rigid active site, optimization of ligands in the active site with implicit solvation, and optimization of ligands in the active site using relaxed amino acid side chains (non-rigid) and implicit solvation.[1] In the current work, we use our previously validated solvated-relaxed model to examine the effects of *in silico* site-directed mutagenesis of two amino acid residues within the SULT1A3 active site—D86 and E146—on ligand binding. These computational results are then compared with experimental mutagenesis results (E146).[2] Dopamine, two dopaminergic analogues, and resveratrol were the ligands chosen for study (Fig. 1).

Sulfotransferases are involved in the metabolism of xenobiotics, as well as endogenous substrates.[3] The sulfation of these molecules improves their water solubility, thus affecting excretion and transport.[3] The amino acid residue His108, which is highly conserved in the SULT family, is involved in the catalysis of the sulfation reaction through the abstraction of a proton from the hydroxyl group on the ligand.[3] Lys106 stabilizes the hydroxyl group and increases the ease of deprotonation.