Lipase-catalyzed acylation of (*R,S*)-propranolol: effect of the acyl group on the chemoselectivity

Gilberto A. Zapata Romero, Markus Doerr, Martha C. Daza

Escuela de Química, Universidad Industrial de Santander, Carrera 27 Calle 9, Bucaramanga, Colombia

Experimentally, the acetylation of (*R,S*)-propranolol, catalyzed by Candida antarctica lipase B (CalB) in toluene exhibits enantiopreference (E=63) for (*R*)-propranolol and 100% chemoselectivity for the hydroxy group of propranolol. In the present computational study, we explore the possibility to control the selectivity of this reaction by modifying the size of the acyl group. We focus on the effect of the elongation of ethanoyl hydrocarbon chain on the selectivity. To this end we examine the selectivity of acylation of propranolol using butanoyl, octanoyl and hexadecanoyl groups, analyzing the Michaelis complexes between each serine-acylated CalB and each propranolol enantiomer. Sampling of the Michaelis complex conformations (MCCs) is done using a two step methodology: First, we use ensemble docking and consensus scoring to generate a set of thermodynamically stable MCCs. Second, we collect structurally diverse MCCs to employ them as initial conditions to run multiple molecular dynamics (MD) simulations using diverse initial atom velocity distributions. In the MD simulations, we model the system employing a quantum mechanics/molecular mechanics approach. The set of MCCs obtained from the trajectory of the MD simulations was structurally analyzed. The experimentally observed enantioselectivity of the acetylation could not be reproduced by this protocol. However, we found a correlation with the chemoselectivity toward the hydroxy group. We predict that modifying the chain length of the acyl group gradually inverts the chemoselectivity, i.e., for the longer acyl groups the acylation of the amine group is preferred for both enantiomers.

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