Enantioselectivity of the O-acylation of (*RS*)-atenolol catalyzed by *Candida antarctica* lipase B: effect of the length of the acyl donor

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Acetylation of (R,S)-atenolol, catalyzed by lipase B from *Candida antarctica* (CalB), is selective for O-acylation of (R)-atenolol [J. Mol. Catal. B Enzym.71(3-4), 124-132 (2011)]. The active site of CalB is composed of a catalytic triad, Ser105-His224-Asp187, an oxyanion hole, a large pocket (L-pocket) and a medium pocket (M-pocket). During catalysis, the fast-reacting enantiomer of secondary alcohols places its medium-sized substituent in the M-pocket and its large substituent towards the active-site entrance [ChemBioChem, 6(6), 1051-1056 (2005)]. With the aim to improve the enantioselectivity of CalB in atenolol acylation, we investigated the effect of modifying the length of the acyl group. We performed a series of quantum-mechanical/molecular-mechanical (QM/MM) dynamics simulations of the enzyme-substrate complexes for ethanoyl-, butanoyl-, octanoyl- and hexadecanoyl-CalB with (R)- and (S)-atenolol. The conformations were clustered, using principal component analysis, in order to determine the binding modes of (R)- and (S)-atenolol within the active site of CalB. Our results indicate that the enantioselectivity changes from R-selective to be S-selective as the acyl group length increases. We attribute the inversion of the enantioselectivity to the presence of the acyl group, which destabilizes the placement of the large substituent of (R)-atenolol.