Comparison of reaction coordinates in the enantioselective step of the acetylation of (*R,S*)-propranolol catalyzed by *Candida antarctica* lipase B

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Propranolol ((*R,S*)-1-iso-propylamino-3-(1-naphthoxy)-2-propanol) is a beta-adrenergic blocking agent used for treatment of arterial hypertension and other cardiovascular disorders. Propranolol is commercially available as a racemic mixture. However, only the *S*-enantiomer has the desired therapeutic effect, and administration of the racemic propranolol mixture may cause side effects.

In a previous study *Candida antarctica* lipase B (CalB) was used to carry out the acetylation of (*R,S*)-propranolol with vinyl acetate in toluene [1]. The enantioselectivity was moderate. It originates from the second reaction step, in which the acyl-enzyme transfers an acyl group to the substrate. This step proceeds via an initial Michaelis complex (MCC) and a tetrahedral intermediate (TI).

With the aim to gain a deeper understanding of the molecular basis for the observed enantioselectivity we performed QM/MM explorations of the potential energy surface (PES) between the TI and the MCC and product-CalB complexes.

The QM part of the system was treated at different levels of theory: i) density functional theory employing the B3LYP functional, ii) the semiempirical method SCC-DFTB. For the MM part the CHARMM22 force field was employed. Various reaction coordinates were tested and the shape of the PES and structural parameters were analyzed.

References

1. Escorcia AM, Molina D, Daza MC, Doerr M. Acetylation of (*R,S*)-propranolol catalyzed by *Candida antarctica* lipase B: An experimental and computational study. *J Mol Catal B Enzym*. 2013;98:21-29.