Acetylation of (*R,S*)-propranolol catalyzed by *Candida antarctica* lipase B - exploration of the potential energy surface using density functional theory and semiempirical methods

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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 explorations of the QM/MM 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) semiempirical methods (AM1, OM2, OM3, PM3, SCC-DFTB). The MM part was treated using the CHARMM22 force field.

The aim of this study was to find the most suitable semiempirical method for studying the reaction. To this end the shape of the PES and some important structural parameters were analyzed. It is found that the SCC-DFTB method yields results which are most similar to those obtained at the DFT level.

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.