Substrate-Enzyme Interaction in Pig Liver Esterase

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Force field and first principles molecular dynamics simulations on complexes of pig liver esterase (pig liver isoenzymes and a mutant) and selected substrates (1-phenyl-1-ethyl acetate, 1- phenyl-2-butylacetate, proline-{\beta}-naphthylamide and methyl butyrate) are presented. By restrained force field simulations the access of the substrate to the hidden active site was probed. For a few substrates spontaneous access to the active site via a well defined entrance channel was found. The structure of the tetrahedral intermediate was simulated for several substrates and our previous assignment of GLU 452 instead of GLU 336 was confirmed. It was shown that the active site readily adapts to the embedded substrate involving a varying number of hydrophobic residues in the neighborhood. This puts into question key-lock models for enantioselectivity. Ab initio molecular dynamics showed that the structures we found for the tetrahedral intermediate in force field simulations are consistent with the presumed mechanism of ester cleavage. Product release from the active site as final step of the enzymatic reaction revealed to be very slow and took already more than 20ns for the smallest product, methanol.

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