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THE MECHANISM OF CHOLINESTERASE REACTIONS WITH ORGANO-PHOSPHORUS QUASISUBSTRATES AND ESTER SUBSTRATES

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The leaving groups of organophosphorus compounds and carboxylic esters are differently located in the active centers of cholinesterases that is connected with the stereochemical regularities of the nucleophilic displacement reactions occurring at the carboxyl and phosphoryl groups of these reagents. This different spatial location of quasisubstrates in the enzyme active center also reveals in the mechanism of the bond-breaking steps leading to the formation of the covalent enzymereagent intermediate. In the present communication the mechanism of these reaction steps is discussed with the implication of the putative structures of the transition states. The analysis is based on the results of QSAR for the leaving group effects of ester substrates and organophosphorus quasisubstrates in their reactions with acetylcholinesterase and butyrylcholinesterase. It has been found that the sensitivity of the enzyme phosphorylation rate against the inductive effect of the quasisubstrate leaving group was remarkably high pointing to the complete separation of charges in the transition state. On the other hand, the transition state of the butyrylcholinesterase acylation reaction has been found to be similar to the structure of the appropriate acyl-enzyme. Besides these two enzymes the reactions of ester substrates and organophosphorus quasisubstrates have been studied with a covalently modified derivative of acetylcholinesterase, synthesized by affinity labelling of the native enzyme with N,N-dimethyl-2-phenylaziridinium ions. The data obtained allow to discuss the role of the putative "anionic point" of acetylcholinesterase in the enzyme reactions with organophosphorus quasisubstrates and ester substrates.