

MEETING ABSTRACTS

THE CATALYTIC POWER OF PHOSPHOTRIESTERASES FOR THE HYDROLYSIS AND DESTRUCTION OF ORGANOPHOSPHORUS NERVE AGENTS

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Phosphotriesterase (PTE), an enzyme originally isolated from *Pseudomonas diminuta*, is capable of catalyzing the hydrolysis of many organophosphorus nerve agents. The turnover number for the enzymatic hydrolysis of paraoxon (diethyl p-nitrophenyl phosphate) by PTE is $\sim 500,000 \text{ min}^{-1}$. The protein adopts a distorted $(\beta/\alpha)_8$ -barrel structural fold and the active site is perched at the C-terminal end of the β -barrel. The water used for nucleophilic attack of the substrate bridges two divalent metal ions in the active site and is further activated by the side chain carboxylate from an aspartate residue that resides at the end of β -strand 8. Upon binding to the active site, substrates are further activated for hydrolysis by a direct interaction of the phosphoryl oxygen with the β -metal ion. The chemical reaction is initiated via the direct attack of the bridging water/hydroxide at the phosphorus center of the substrate and proceeds with an inversion of stereochemistry. Wild-type PTE is stereoselective for the hydrolysis of chiral substrates. However, the catalytic preferences for the hydrolysis of chiral substrates can be enhanced, relaxed, or inverted by selective mutation of key residues in the active site that dictate the size and shape of the substrate-binding cavity. The extreme toxicity and persistence of the G-type (sarin and soman) and V-type (VX and VR) organophosphorus nerve agents makes the detoxification of these compounds of significant interest. A rational and random mutagenesis strategy has been developed and implemented for the evolution of mutant forms of PTE that are more fully optimized for the catalytic destruction and detoxification of the most toxic organophosphorus nerve agents.