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ARTICLE

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Reaction of Cresyl Saligenin Phosphate, the Organophosphorus Agent Implicated in Aerotoxic Syndrome, with Human Cholinesterases: Mechanistic Studies Employing Kinetics, Mass Spectrometry, and X-ray Structure Analysis

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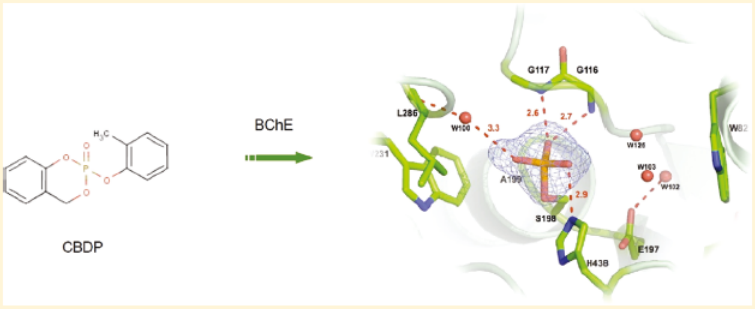
ABSTRACT:



Aerotoxic syndrome is assumed to be caused by exposure to tricresyl phosphate (TCP), an antiwear additive in jet engine lubricants and hydraulic fluid. CBDP (2-(ortho-cresyl)-4*H*-1,2,3-benzodioxaphosphoran-2-one) is the toxic metabolite of triortho-cresylphosphate, a component of TCP. Human butyrylcholinesterase (BChE; EC 3.1.1.8) and human acetylcholinesterase (AChE; EC 3.1.1.7) are irreversibly inhibited by CBDP. The bimolecular rate constants of inhibition (k_i), determined under pseudo-first-order conditions, displayed a biphasic time course of inhibition with k_i of 1.6×10^8 M^{-1} min^{-1} and 2.7×10^7 M^{-1} min^{-1} for E and E′ forms of BChE. The inhibition constants for AChE were 1 to 2 orders of magnitude slower than those for BChE. CBDP-phosphorylated cholinesterases are nonreactivatable due to ultra fast aging. Mass spectrometry analysis showed an initial BChE adduct with an added mass of 170 Da from cresylphosphate, followed by dealkylation to a structure with an added mass of 80 Da. Mass spectrometry in ^{18}O-water showed that ^{18}O was incorporated only during the final aging step to form phospho-serine as the final aged BChE adduct. The crystal structure of CBDP-inhibited BChE confirmed that the phosphate adduct is the ultimate aging product. CBDP is the first organophosphorus agent that leads to a fully dealkylated phospho-serine BChE adduct.