Modes of nucleophilic attack on O,S-dimethyl methylphosphonothiolate using normal and alpha nucleophiles

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One of the most potent chemical warfare agents is the nerve agent O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate (Agent VX), an organophosphorus ester capable of entering the human body both by inhalation and by skin contact. Once inside the body, Agent VX covalently binds to acetylcholinesterase, the enzyme responsible for degrading acetylcholine. This causes a buildup of acetylcholine and results in loss of muscle control and ultimately death by respiratory failure. Detoxification of VX occurs when the P-S bond is cleaved. Hydrolysis has been shown to give a mixture of P-S and P-O cleavage, with the latter resulting in the formation of the toxic S-(2-diisopropylamino)ethyl methylphosphonothiolate ion. Hydroperoxidolysis, by contrast, uses an alpha-nucleophile and leads exclusively to P-S cleavage. This reaction could proceed via S_N2 attack on either the alkoxide or alkylthiolate ligands, or addition-elimination at the phosporyl phosphorus. However, because this reaction takes place in aqueous hydroperoxide solution, oxidation of the sulfur atom in VX could precede neutralization. Using the model compound O,S-dimethyl methylphosphonothiolate (O,S-DMMP), a simulant for VX, computational studies at the M05-2X/6-31+G(d,p) level of theory with the IEF-PCM solvation model have been carried out to gain a greater understanding of these solvolysis mechanisms by determining the potential energy surfaces and stationary points for both the hydrolysis and hydroperoxidolysis reactions in aqueous solution.