CONFORMATIONAL ANALYSIS OF TOXOGONINE, TMB-4 AND HI-6 BY PM6 AND RM1 METHODS

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The nerve agents are esters of the phosphoric acid acting as potent inhibitors of acetylcholinesterase (AChE) by a very fast phosphylation reaction that can lead to an irreversible inhibition. However, this inhibition can be avoided by a nucleophile, usually an oxime. Despite the existence of many different oximes in use today against neurotoxic agents, it has not been reported yet any universal one, once oximes that are efficient for the treatment of intoxication with one specific nerve agent can be completely ineffective with another. This probably happens because their mechanisms of action are not well elucidated yet. Some relevant factors like the adequate orientation of the phosphoryl bond inside the active site, the suitable oxime's charge and conformation and, also, their angles for attacking the phosphylated AChE remain unknown. In the present work, in order to make an additional contribution to these studies, we performed conformational analysis studies by semi-empirical methods for the determination of the stable conformers varying two dihedrals ($?_1$ and $?_2$) in the oximes: Toxogonine, TMB-4, and HI-6, followed by vibrational analysis of the stationary points for true energy maxima search by RM1, PM6 and DFT/B3LYP/6-31 +G (d,p). Results show that each oxime has stable structures and one unique imaginary frequency. In addition, we confirmed the transition state localization and this might be useful for posterior molecular parameterizations of these molecules in further molecular modeling studies of their mechanisms of action.

Keywords: Acetylcholinesterase, Conformational Analysis, Oximes, Neurotoxic agents.

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