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## Phosphonylated Acetylcholinesterase as Transition State Analogs: The Anticholinesterase Properties of Halomethylphosphonates

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## Phosphonylated Acetylcholinesterase as Transition State Analogs: The Anticholinesterase Properties of Halomethylphosphonates

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The  $\text{CH}_3\text{P}(\text{O})$  moiety of methylphosphonates of the type  $\text{CH}_3\text{P}(\text{O})(\text{OR})\text{X}$ , I, may play an important role in the effective binding to the appropriate hydrophobic patch in the active site of acetylcholinesterase (AChE), in analogous manner to the acetyl residue,  $\text{CH}_3\text{C}(\text{O})$ , of the substrate acetylcholine which determines substrate specificity. Since the substitution of halide atom for hydrogen in I is expected to introduce electronic, steric and hydrophobic changes, it was interesting to study the effect of such a substitution on both the inhibition of AChE and the stability of the phosphonylated enzyme. A significant decrease in the stability of the enzyme conjugates,  $\text{YCH}_2\text{P}(\text{O})-(\text{OisoPr})\text{O-AChE}$  ( $\text{Y}=\text{Cl}, \text{Br}, \text{I}$ ) was observed in terms of an increase in the rate constants of the spontaneous and induced reactivations as well as the aging process relative to the non-substituted molecule where  $\text{Y}=\text{H}$ . The electron withdrawal effect of the halogen atom alone, cannot explain the changes in the anti-ChE properties of the halomethylphosphonates when compared to the non-substituted inhibitor. These results are in accord with the view that the phosphonylated enzyme may be considered as a transition-state analog for the hydrolysis of an acylated enzyme (Ashani and Green in "Studies in Organic Chemistry", pp 169-188, Vol 10, Elsevier, 1981). It is further concluded that in contrast to the  $\text{OP-AChE}$  conjugates the OP themselves cannot be rationalized in terms of transition-state analogs.