

Method to Evaluate Mechanism of Reaction of a Former War Gas that has Found Applications in Medicine

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Background: In 1915 Phosgene was first employed as a war gas because it readily dissolved in Acetone to form Isopropenyl Chloroformate, which undergoes rapid hydrolysis to produce corrosive HCl. Recently Isopropenyl Chloroformate was used in the esterification of peptidyl p-Methoxybenzoic Acid. This knowledge has been applied to the development of selective inactivators for serine proteases that have been shown to play major roles in human health.

Methods: The specific rates of solvolysis Isopropenyl Chloroformate are analyzed using Linear Free Energy Relationships such as the Grunwald-Winstein equations.

Results: Previous studies found that Alkyl Chloroformates solvolyze by an addition-elimination mechanism with the addition step being rate-determining. In fluoroalcohols the mechanism changed to ionization, therefore we expanded previous kinetic studies of Isopropenyl Chloroformate to include 1,1,1,3,3,3- Hexafluoro-2- Propanol (HFIP) and 2,2,2-Trifluoroethanol (TFE).

Conclusions: The relatively fast reaction of Isopropenyl Chloroformate versus the Isopropyl analog in MeOH and EtOH, shows that the alkenoxy substituent exerts a powerful inductive influence. Unlike the solvolyses of Isopropyl Chloroformate which show a dichotomy of behavior as the solvent is varied, the addition-elimination mechanism dominates over the full range of solvent composition for Isopropenyl Chloroformate.

[This project was supported by NIH NCRR INBRE grant number; 2 P20 RR016472-07]