

MEETING ABSTRACTS

STERIC EFFECTS IN THE DECARBAMOYLATION OF CARBAMOYLATED ACETYLCHOLINESTERASE

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Carbamates are esters of substituted carbamic acids that react with acetylcholinesterase (AChE) in a two-step process, with initial transfer of the carbamoyl acyl group to a serine residue of AChE accompanied by loss of the carbamate leaving group followed by hydrolysis of the carbamoyl enzyme. This hydrolysis, or decarbamylation, is relatively slow, and half-lives of carbamoylated AChEs range from 4 min to more than 30 days. Since carbamates are poor, slowly reversible AChE substrates, they are effective AChE inhibitors that have been developed as insecticides and therapeutic agents. We show that decarbamylation rates are independent of the leaving group for a series of carbamates with the same carbamoyl group. For a given leaving group, when the alkyl substituents on the carbamoyl group increased in size from *N*-monomethyl- to *N,N*-dimethyl-, *N*-ethyl-*N*-methyl-, or *N,N*-diethyl-, the decarbamylation rates decreased by 4-, 70-, and 1000-fold, respectively. Thus the larger the size of the alkyl groups, the slower the rate of decarbamylation due to active site distortion. Furthermore, solvent deuterium oxide isotope effects for decarbamylation decreased from 2.8 for *N*-monomethylcarbamoyl AChE to 1.3 for *N,N*-diethylcarbamoyl AChE, indicating a shift in the rate-limiting step from general acid-base catalysis to a likely conformational change.

Keywords: Acetylcholinesterase; Decarbamylation; N,N-diethyl carbamates