Synthesis and Chemical Stability of L-Citrulline Ethyl Ester Across Alkaline Conditions

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L-citrulline is a nonessential a-amino acid involved in both the urea and nitric oxide cycles and is commonly used as a supplement to increase peripheral vasodilation. However, its high polarity limits intestinal absorption and bioavailability. To improve lipophilicity, citrulline was converted into its ethyl ester via the Fischer-Speier esterification process. Its chemical stability was evaluated under alkaline conditions (pH 9-11) relevant to esterase activity. Base-catalyzed hydrolysis of the ester was monitored with titrimetric analysis at 37 °C. Hydrolysis followed pseudo-first order kinetics, with rate constants varying across pH conditions (0.0359 at pH 9, 0.0310 pH 10, and 0.0258 at pH 11). One-way ANOVA indicated a statistically significant difference in hydrolysis rates among pH conditions ($p = 0.00366$, $a = 0.01$), demonstrating that esterification is correlated with increased rates of base-catalyzed hydrolysis, and that stability of the ester is pH-dependent. Increased lipophilicity of the ester derivative enhances the membrane permeability prior to ester cleavage, allowing the compound to function as a prodrug that gradually regenerates L-citrulline. Comparison with pharmacokinetic profiles of free L-citrulline therefore suggest that controlled hydrolysis of the ester could produce a comparable peak in nitric oxide production while prolonging the duration of elevated plasma citrulline levels through sustained release of the parent amino acid. These findings provide insight into the chemical behavior of citurlline ester derivatives and their potential application as prodrugs for improving citurlline bioavailability.

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