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ENZYMATIC OLIGOMERISATION VERSUS LACTONISATION OF ω-HYDROXYESTERS

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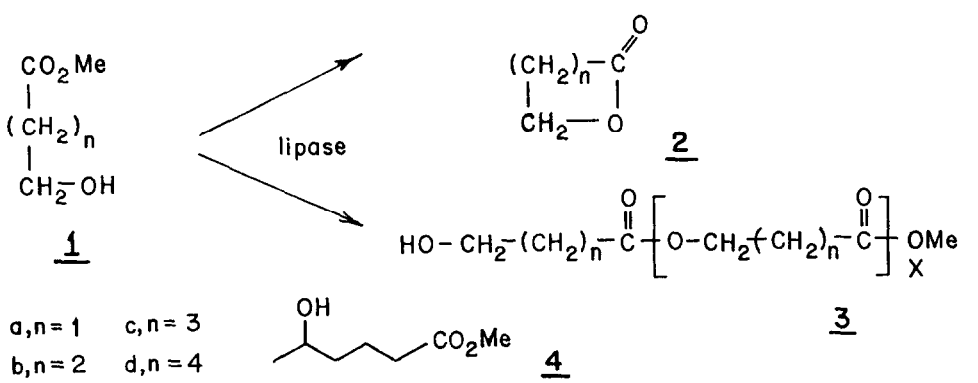
Summary: Porcine pancreatic lipase in anhydrous organic solvents catalyses almost exclusively the oligomerisation reaction of unsubstituted β, δ, and ε-hydroxyacid methyl esters. In contrast, the substituted δ-methyl- δ-hydroxyester undergoes lactonisation.

Recent data have shown that enzymes can function also in organic solvents and, under certain experimental conditions, they are even more stable than in aqueous media[1]. A.M. Klibanov et al[2]. have reported that some lipases catalyse reactions of esterification and transesterification in nearly anhydrous solvents. We have shown[3] that porcine pancreatic lipase can act as a practical and highly stereoselective catalyst for intramolecular transesterification of γ-hydroxyesters and have used this method to prepare gram quatities of optically pure substituted γ-lactones. Recently, Yamada et al[4]. reported that lipases catalyse lactonisation of highly diluted solutions of long-chain ω-hydroxyacids methyl esters. Their paper prompts us to publish our findings to date on the behaviour of β, δ, and ε-hydroxyesters with porcine pancreatic lipase.

The dependence of the lactone-to-oligomer ratio on the chain-length of acid catalysed ω-hydroxyesters has been well established[5]. If the ring size is less than five atoms or more than seven, the product consists almost entirely of open chain polymer. If a ring containing five annular atoms can be formed, this is the exclusive product; if of six or seven atoms, either the ring or the chain polymer is formed - or both. We now wish to report that when unsubstituted β, δ and ε-hydroxyesters 1[6] are submitted to the action of porcine pancreatic lipase in organic solvents, they exclusively undergo intermolecular transesterification to afford the corresponding oligomers 3.



The following experiment is representative: 0.5 g of the powdered commercial preparation of porcine pancreatic lipase (E.C. 3.1.1.3)[7] was added to solution of 440mg (3.3 mmol) methyl δ-hydroxyvaleric acid **1c** in 20 ml dry ether in a conical flask equipped with a drying tube, and the suspension was shaken on a reciprocal shaker at 100 rpm at 26°C. Aliquots were withdrawn periodically and examined by 400 MHz NMR spectroscopy with the purpose of detecting the following four groups of signals: (I) - singlet at 3.65 ppm common to the esteric methyl protons of **1c** and of **3c**; (II) - triplet at 4.25 ppm corresponding to the δ-methylene protons of the δ-lactone **2c**; (III) - triplet at 3.55 ppm corresponding to the δ-methylene protons adjacent to a hydroxyl, as in **1c**, or the terminal $HOCH_2$- in **3c**; and (IV) - triplet at 4.00 ppm corresponding to the esteric δ-methylene protons $-\overset{O}{\overset{\|}{C}}-O-CH_2-$ of the oligomer **3c**. Progress was monitored to within ±10% accuracy by comparing the NMR integration of the above-mentioned signals. It was revealed, that there was no formation of δ-valerolactone (**2c**) (no signal detected near 4.25 ppm), but there was a gradual conversion of **1c** into the oligomer **3c**: signal (IV) increased at the expense of signals (I) and (III). The reaction was terminated after 120 hr by filtering out the enzyme: at this point the ratio of integrals of the NMR signals (IV):(I) and (IV):(III) suggested that the oligomer **3c** was on avarage a heptamer (x=6).

Similar results were obtained with methyl β-hydroxypropionate (**1a**) and with methyl ε-hydroxycaproate (**1d**). It was possible to divert the enzymatic reaction of **1c** towards the formation of **2c** by conducting the condensation at very high dilution (1 mg/ml), where the opportunity for intermolecular reaction is less favourable[8]. In contrast, the secondary alcohol, δ-methyl- δ-hydroxyester (**4**)[9] cleanly underwent lactonisation even in concentrated solutions. Furthermore, similarly to the behaviour of γ-hydroxyesters[3], the reaction considerably slowed down near 50% conversion, indicating that the process was enantioselective. This drastic effect of δ-substitution, which tips the balance in favor of lactonization, is being investigated further.

Oligomerisation of ω-hydroxyesters provides a powerful new addition to porcine pancreatic lipase's utility in organic solvents. Working with suitably substituted hydroxyesters, we are now investigating the stereoselectivity of this reaction and its potential for the preparation of optically active polyesters from racemic monomers.

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