Molecular simulation of receptor/substrate interaction: the case of alpha-chymotrypsin and beta-carboethoxy-gamma-lactames

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A number of compounds containing the gamma-lactam (pyrrolidin-2-one) moiety show interesting biological and pharmacological activities, and are key intermediates in the synthesis of antibiotics and naturally occurring compounds. For instance, they are used as psychotropic and anti-hypertensive agents, muscarinic acid antagonists and GABA (g-aminobutyric acid) analogs. Despite their intrinsic potentiality for biological activity, those derivatives of gamma-lactams carrying a carboxylic functionality in the beta position have received scarce attention, especially in their optically active form.

Recently, alkyl esters of such derivatives, N-substituted with different functional groups, have been treated for kinetic resolution with hydrolytic enzymes such as esterases, lipases and proteases. In particular, alpha-chymotrypsin (alpha-CT) has been shown to hydrolyze with high enantioselectivity and in an enantiocomplementarity fashion the lactam derivative 1 (methyl 1-benzyl-5-oxo-3-pyrrolidincarboxylate), 2 (methyl 1-(2-hydroxyethyl)-5-oxo-3-pyrrolidincarboxylate) and 3 (methyl 1-isopropyl-5-oxo-3-pyrrolidincarboxylate), yielding the enantiomer (3S)-(−)-1 with 95% ee, (3R)-(−)-2 with 99% ee and (3R)-(−)-3 with 96% ee, respectively. On the contrary, the same enzyme has shown no enantioselectivity for derivative 4 (methyl 5-oxo-3-pyrrolidincarboxylate), which can be recovered in racemic form from the hydrolytic process.

To understand and elucidate the origins of these diversities and, particularly, the reasons for lactam enantioselectivity of alpha-CT, we have performed a detailed molecular simulation study focused on (a) the investigation of the molecular interactions and inclusion phenomena of compounds 1 - 4 at the active site of alpha-CT and (b) the evaluation of the interaction energies and analysis of the energetic contributions in the resulting complexes.