Kinetic Models of Cyclosporin A and Cyclosporin E to Rationalize Membrane Permeability

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The membrane permeability of cyclic peptides is strongly influenced by the conformational behaviour in polar and apolar environments. The size and complexity of peptides often limits their bioavailability, but there are known examples of peptide natural products that can cross cell membranes by passive diffusion. One of them is Cyclosporin A (CsA), used as a drug preventing transplant rejection [1]. CsA is an undecapeptide with seven methylated backbone amides. Its synthetic derivative, Cyclosporin E (CsE), lacks Val-11 *N*-methylation and its membrane permeability is one order of magnitude lower [2].

The aim of presented work is to rationalize the structural and kinetic differences between CsA and CsE leading to different permeability, using molecular dynamics simulations and Markov state models. Computational results are compared to experimental NMR data. The results suggest that the membrane permeability of cyclic peptide is connected to its ability to form "congruent" conformational states, i.e. conformational states significantly populated both in polar and apolar environments [3]. These findings may provide insights for the rational design of novel cyclic peptides for pharmaceutical industry.

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